CLINICAL PHARMACOLOGY and THERAPEUTICS

*volume* 2 *number* 6 **November-December 1961**

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# *earlier detection of peripheral vascular disease*
# *key to improved therapeutic response*

In practically all peripheral vascular disease cases where marked occlusion with severe ulceration or frank gangrene has not developed, patients can be assured that excellent treatment is available and many symptoms can be relieved.[1] Routine palpation of peripheral pulses[2] and performance of clinical tests for peripheral arterial disease[3] will help earlier diagnosis. Consequently treatment can be instituted sooner, improving likelihood of a favorable response to therapy.

# VASODĪLAN®

*Isoxsuprine hydrochloride, Mead Johnson*

myo-  -vascular relaxant

## increases deep peripheral circulation by direct action ...without troublesome side effects

VASODĪLAN'S record of safety and effectiveness in the management of peripheral vascular disease has been established clinically.[4-6] Clarkson and Le Pere report: "With strictly a clinical office approach, isoxsuprine [VASODĪLAN] was used in the treatment of 100 patients with peripheral vascular disorders. Definite clinical improvement was obtained in 89 per cent of these patients."[5] They further state: "In particular, the symptoms of pain, cramping, numbness, and cold were consistently relieved."[5]

*Contraindications* – There are no known contraindications to oral administration of VASODĪLAN in recommended doses.

*Cautions* – VASODĪLAN should not be given immediately postpartum or in the presence of arterial bleeding. Parenteral administration is not recommended in the presence of hypotension or tachycardia. Intravenous administration is not recommended because of the increased likelihood of side effects.

*Side effects* – Few side effects occur when given in recommended doses. Occasional palpitation and dizziness can usually be controlled by dosage adjustment. Single intramuscular doses of 10 mg. or more may result in hypotension or tachycardia.

*Dosage and administration* – Oral – 10 to 20 mg. (1 to 2 tablets) t.i.d. or q.i.d.; I.M. – 5 to 10 mg. b.i.d. or t.i.d.

*Supplied* – 10 mg. tablets, bottles of 100; 2 cc. ampuls (5 mg./cc.) for intramuscular use, boxes of 6.

For complete details on indications, dosage, administration and clinical background of VASODĪLAN, see the brochure of this product available on request from Mead Johnson Laboratories, Evansville 21, Indiana.

*References:* (1) Lieberman, J. S.: GP *21*:133-143 (March) 1960. (2) DeWeese, J. A.: New England J. Med. *262*:1214-1217 (June 16) 1960. (3) Winsor, T.: Peripheral Vascular Diseases: An Objective Approach, Springfield, Illinois, Charles C Thomas, 1959, pp. 457-458. (4) Kaindl, F.; Samuels, S. S.; Selman, D., and Shaftel, H.: Angiology *10*:185-192 (Aug.) 1959. (5) Clarkson, I. S., and Le Pere, D. M.: Angiology *11*:190-192 (June) 1960. (6) Samuels, S. S., and Shaftel, H. E.: J.A.M.A. *17*:142-145 (Sept. 12) 1959.

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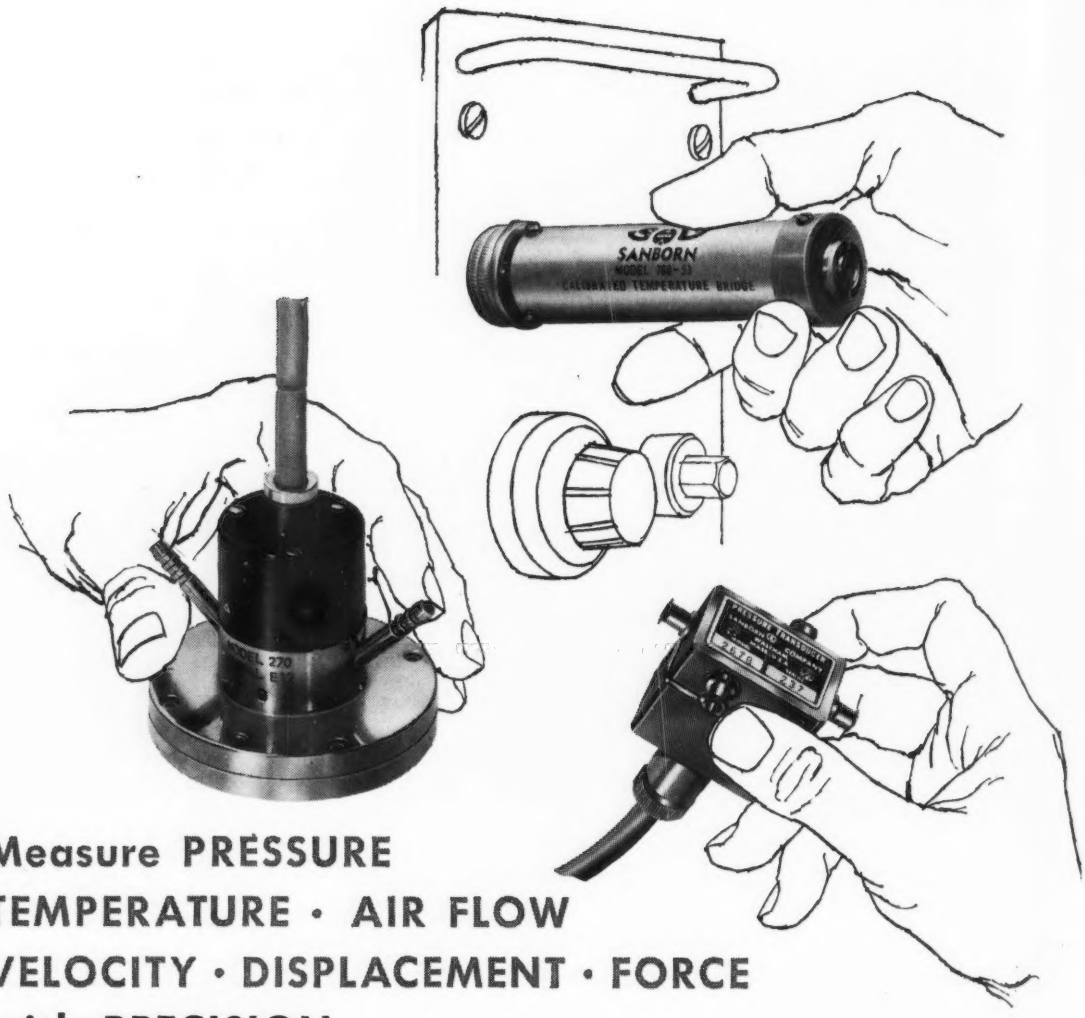
*Volume 2, Number 6, November-December, 1961, CLINICAL PHARMACOLOGY AND THERAPEUTICS. Published bimonthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Second class postage paid at St. Louis, Mo. Subscription rates: United States and its possessions $12.50; Canada, Latin America, and Spain $13.50; other countries $14.00. Students, interns, and resident physicians: United States and its possessions $7.50; Canada, Latin America, and Spain $8.50; other countries $9.00. Single copies $2.50 postpaid.*

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CLINICAL PHARMACOLOGY and THERAPEUTICS



*Continued on page 7*

# CLINICAL PHARMACOLOGY and THERAPEUTICS

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*3207 Washington Boulevard*
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# clinical experience continues to corroborate the range and efficacy of

# CYTOXAN®

*Cyclophosphamide, Mead Johnson*

## CYTOTOXIC AGENT for palliative chemotherapy of certain types of malignant neoplasms

Cytoxan demonstrated therapeutic advantage over other agents in a recent 12-month study* of 130 patients, most of whom were refractory to previous treatment:

| DISEASE | NUMBER OF PATIENTS | RESULTS | | | | INADEQUATE TRIAL |
|---|---|---|---|---|---|---|
| | | GOOD | FAIR | TRANSIENT | FAILURE | |
| **Lymphoma** | **74** | **34** | **3** | **5** | **23** | **9** |
| Hodgkin's Disease | 29 | 10 | 3 | 4 | 9 | 3 |
| Lymphosarcoma | 21 | 15 | 0 | 0 | 3 | 3 |
| Multiple Myeloma | 16 | 9 | 0 | 0 | 4 | 3 |
| Reticulum Cell Disease | 8 | 0 | 0 | 1 | 7 | 0 |
| **Leukemia** | **23** | **10** | **0** | **0** | **8** | **5** |
| Chronic Lymphatic Leukemia | 8 | 4 | 0 | 0 | 3 | 1 |
| Acute Monoblastic Leukemia | 11 | 5 | 0 | 0 | 3 | 3 |
| Acute Myeloblastic Leukemia | 4 | 1 | 0 | 0 | 2 | 1 |
| **Carcinoma (Breast, Lung, and Solid Tumors)** | **29** | **2** | **1** | **1** | **23** | **2** |
| **Miscellaneous (Mycosis, Fungoides, Psoriasis)** | **4** | **0** | **0** | **1** | **3** | **0** |
| Total | 130 | 46 | 4 | 7 | 57 | 16 |

*Adapted from Wall, R. L., and Conrad, F. G.*

Note that the neoplastic disorders most responsive to Cytoxan were lymphosarcoma, multiple myeloma, Hodgkin's disease, and chronic lymphatic leukemia. Occasionally, good results were observed in acute monocytic leukemia and carcinoma of the breast.

***Other advantages noted in this study****

• multiple routes of administration, permitting prolonged maintenance therapy • lack of latency period for bone marrow depression • failure to produce significant thrombocytopenia • potential therapeutic effect in diseases usually unresponsive to other mustard compounds (*e.g.*, myeloma).

*Wall, R. L., and Conrad, F. G.: Arch. Int. Med. *108*:456-482, 1961.

**INDICATIONS:** Cytoxan is valuable for palliative therapy of certain malignant neoplasms, particularly some of those arising in the reticuloendothelial and hematopoietic systems and certain solid tumors.

Types of cancer which have proved relatively more susceptible or more resistant to Cytoxan therapy may be grouped as follows:

Group I: Neoplasms relatively susceptible to Cytoxan
- Hodgkin's disease
- Lymphomas: lymphosarcoma; giant follicular lymphoma; reticulum cell sarcoma
- Leukemia: acute; chronic
- Mycosis fungoides

Group II: Neoplasms relatively resistant to Cytoxan
- Malignant neoplasms of the breast and the ovary*
- Malignant neoplasms of the lung, the gastrointestinal tract and the genitourinary system, including the cervix and the uterus
- Malignant neoplasms of miscellaneous origin
- Malignant melanomas

*Malignant tumors of these organs are somewhat more susceptible to Cytoxan therapy than are the others included in this group.

**DOSAGE:** *For neoplasms relatively susceptible to Cytoxan* —Patients with lymphomas and other neoplasms believed to be relatively susceptible to Cytoxan therapy are given an initial dose of 2 to 3 mg./Kg./day intravenously. White blood counts and platelet determinations should be made daily or twice weekly and the dosage adjusted accordingly. Intravenous infusions should be continued for at least 6 days unless otherwise indicated. A leukopenia of between 1500 and 5000 cells per cu. mm. (or lower) may be expected between the tenth and fourteenth day. In the presence of a leukopenia of less than 2000/cu. mm. Cytoxan should be discontinued until the white cell count returns to 2000 to 5000 (usually within a week). Dosage is subsequently adjusted as indicated by the patient's objective response and the leukocyte count. If the patient is subjectively improved, if the size of the tumor has decreased, or if the white cells are satisfactorily maintained between 2000 and 5000/cu. mm. oral dosage may be instituted equivalent to intravenous dosage.

Thrombocytopenia is rarely observed on this regimen. If platelet counts of less than 100,000/cu. mm. are observed, the patient should be watched carefully. If platelets continue to decrease, Cytoxan should be discontinued.

The patient who has had previous treatment with alkylating agents, or x-ray, or is debilitated may be more susceptible to bone marrow depression, and initial Cytoxan doses should be more conservative than the above. Such patients should have more frequent hematologic evaluation. Good medical practice demands access to a reliable hematologic laboratory when using Cytoxan.

*For neoplasms relatively resistant to Cytoxan* —Patients with carcinomas and other malignant neoplasms believed to be less susceptible to Cytoxan therapy are given a dose of 4 to 8 mg./Kg./day intravenously. Unless there are indications to the contrary, this dose is continued for 6 days, then stopped. Leukopenia usually ensues on the tenth to fourteenth day after the first dose of Cytoxan. Thrombocyte reduction is not common, and platelets may actually increase. The leukocyte count promptly returns toward normal levels in most cases, and as it begins to increase, sufficient Cytoxan is administered to maintain it near 2000 to 5000/cu. mm. This may be accomplished by two intravenous injections weekly, or by oral administration, or by a combination of both routes. An oral dosage of 50 to 200 mg. daily or an intravenous injection of 5 mg./Kg. twice weekly will usually suffice.

The platelet and leukocyte counts should be followed carefully, and the prior treatment history of patients carefully evaluated as delineated above.

*Leukopenia as a guide to adequacy of dosage* —The best objective measure for dosage seems to be the number of circulating white blood cells. This is used as an index of the activity of the hematopoietic system, especially the bone marrow. The mechanism by which Cytoxan causes a reduction in the level of white blood cells is not known, but cessation of dosage results in an increase in the level, indicating that the hematopoietic system had not been permanently affected. When large doses (8 mg./Kg./day for 6 days) are given initially, the white cell count falls rapidly. Following the cessation of the 6-day course, the white cells may continue to decline for as long as 8 days and then increase. The reduction of the white cell count during Cytoxan therapy and its subsequent increase when therapy is discontinued can be repeated in the same patient. Maximal reduction in leukocyte count indicates the maximal permissible Cytoxan level for therapeutic effect. Leukopenic patients must be watched carefully for evidence of infection.

Total white blood cell and thrombocyte counts should be obtained 2 or more times weekly in order to evaluate therapy and to adjust dosage.

**SIDE EFFECTS:** Although Cytoxan is related to nitrogen mustard, it has no vesicant effect on tissue. It does not traumatize the vein when injected intravenously, nor does it cause any localized tissue reaction following extravasation. It may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally or directly into the tumor, when indicated. It is apparently active by each of these routes.

Nausea and vomiting are common and depend on dose and on individual susceptibility. However, many investigators accept the nausea and vomiting in favor of maintaining maximal therapy. The vomiting can be controlled with antiemetic agents.

Alopecia is a frequent side reaction to Cytoxan therapy. It has been observed in 28% of the patients studied in this country. The incidence is greater with larger doses. The loss of hair may first be noted about the 21st day of therapy and may proceed to alopecia totalis. This effect is reversed following discontinuance of Cytoxan; during reduced maintenance therapy, hair may reappear. It is essential to advise the patient in advance concerning this effect of the drug.

Dizziness of short duration and of minor degree has occasionally been reported.

Leukopenia is an expected effect and can be used as a guide to therapy. Thrombocytopenia may occur, especially after large doses. The leukocyte or platelet counts of an occasional patient may fall precipitously after even small doses of Cytoxan, as with all alkylating agents. The drug should be discontinued in such patients and reinstituted later at lower dosage after satisfactory hematologic recovery has occurred. Prior treatment with x-ray or with other chemotherapeutic agents frequently causes an earlier or exaggerated leukopenia or thrombocytopenia after Cytoxan medication. Only rarely has there been a report of erythrocyte or hemoglobin reduction.

**ADMINISTRATION:** Add 5 cc. sterile water (Water for Injection, U.S.P.) to 100 mg. of Cytoxan in the sterile vial (add 10 cc. to 200 mg. vial). Shake, allow to stand until clear, remove with sterile syringe and needle and inject.

The freshly prepared solution of Cytoxan may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally, or directly into the tumor. The solution should be administered promptly after being made but is satisfactory for use for three hours after preparation.

If the patient is receiving a parenteral infusion, the Cytoxan solution may be injected into the rubber tubing if the solution is glucose or saline.

No thrombosis or thrombophlebitis has been reported from injections of Cytoxan. Extravasation of the drug into the subcutaneous tissues does not result in local reactions.

**PRECAUTIONS:** Cytoxan should not be given to any person with a severe leukopenia, thrombocytopenia, or bone marrow infiltrated with malignant cells. It may be given with suitable precautions to patients who have had recent x-ray treatment, recent treatment with a cytotoxic agent, a surgical procedure within 2 to 3 weeks, or debilitated patients.

**AVAILABILITY:** Cytoxan is available as follows:

Cytoxan for Injection, 100 mg., a sterile dry-filled vial containing 100 mg. cyclophosphamide and 45 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan for Injection, 200 mg., a sterile dry-filled vial containing 200 mg. cyclophosphamide and 90 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan Tablets for oral administration, 50 mg., white, round tablets, flecked with blue for easy identification. Packaged, 100 tablets per bottle.

For a copy of the Cytoxan brochure, or other additional information on Cytoxan, communicate directly with the Medical Department, Mead Johnson Laboratories, Evansville 21, Indiana.

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*Another clinical report from Sunkist:*

# Stress Conditions and Citrus Bioflavonoid Therapy

Capillary damage – increased permeability – is a uniform basic reaction resulting from injury or stressors of various types:

NUTRITIONAL: Malnutrition, toxins, pregnancy, growth.

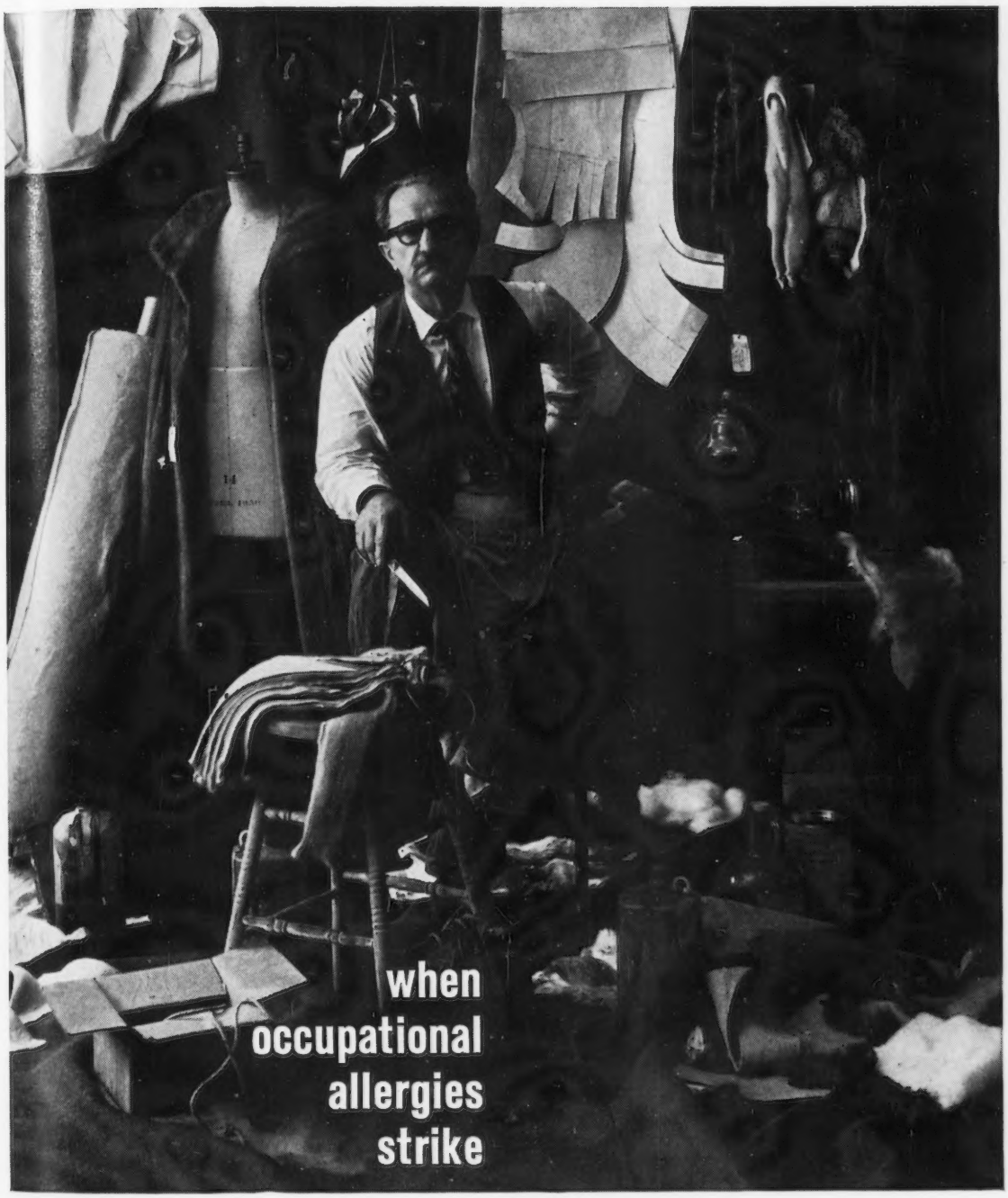
ENVIRONMENTAL: Temperatures, pressure, radiation, allergies.

DISEASE STATES: Viral, bacterial, malignancies, endocrine.

The multiple activities of the citrus bioflavonoids in the prevention or reversal of the inflammatory process include: (1) Maintenance of capillary integrity, (2) In cellular metabolic processes, by potentiating corticosteroids, vitamins and essential nutrients, and by inhibition of hyaluronidase, and (3) Direct anti-inflammatory action.

In the treatment of stress conditions include the citrus bioflavonoids (Lemon Bioflavonoid Complex, Hesperidin Complex and Hesperidin Methyl Chalcone) in the therapeutic regimen.

*FREE: Write for "CITRUS BIOFLAVONOIDS in health and disease"— the comprehensive Sunkist brochure reviewing current bioflavonoid research.*

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## reliably relieve the symptoms...seldom affect alertness

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**A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA**

# NEW
## for the management of
# ASTHMA

# QUIBRON™

Theophylline-glyceryl guaiacolate, Mead Johnson ELIXIR

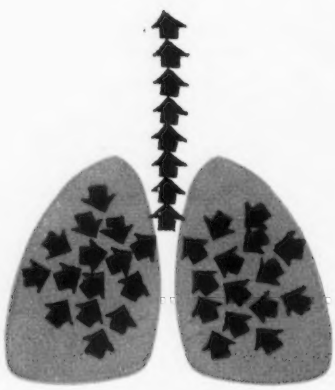
BRONCHODILATOR-EXPECTORANT

## RELAXES CONSTRICTION **by overcoming bronchospasm**

Theophylline overcomes bronchospasm through relaxation of the bronchiolar smooth muscle.

## REDUCES OBSTRUCTION **due to tenacious mucus**

Glyceryl guaiacolate increases respiratory tract fluids which dilute the thick tenacious mucus in the bronchioles, facilitating its removal and thereby reducing obstruction.



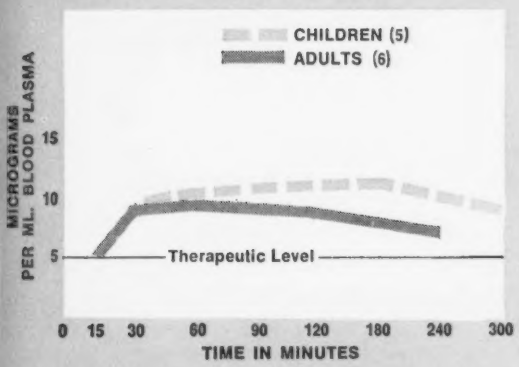
combines the bronchodilator effectiveness of theophylline[1-4]

with the proved expectorant action of glyceryl guaiacolate[5,6]

formulated for flexible low-volume dosage

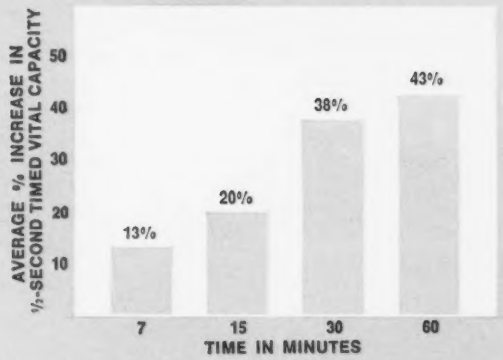
in a pleasant-tasting hydro-alcoholic vehicle for rapid absorption

**QUIBRON RAPIDLY PROVIDES EFFECTIVE THEOPHYLLINE BLOOD LEVELS[7,8]**




Following administration of Quibron elixir at the recommended dosage for adults[7] and children,[8] effective blood levels of theophylline were reached within 15–30 minutes and maintained for more than four hours.

**THERAPY WITH QUIBRON IS FOLLOWED BY RAPID IMPROVEMENT OF VITAL CAPACITY[9]**




Following administration of 20 ml. Quibron elixir, vital capacity was markedly improved, as measured by the timed ½-second method. Pulmonary function tests confirmed the clinical observation of rapid relief occurring in 10-15 minutes in most patients.[9]

***Indications:*** Bronchial asthma, asthmatic bronchitis, chronic bronchitis and pulmonary emphysema.

***Dosage & Administration:*** *Adults:* 1 to 2 tablespoons, 2–3 times daily. *Children, 6–12:* 1 tablespoon, 2–3 times daily. (Children weighing over 100 lbs. may require adult doses.) *Children under 6:* ½ teaspoon per 10 lbs. body weight, 2–3 times daily. During the first day of treatment, especially in severe attacks, the usual dose may be increased by one half.

***Side Effects:*** Theophylline may cause gastric irritation, with possible abdominal discomfort, nausea and vomiting. The administration of Quibron elixir after meals may help avoid such symptoms. Theophylline may also exert some stimulating effect on the central nervous system.

***Cautions:*** Quibron elixir should not be administered more frequently than every 6 hours or within 12 hours after rectal administration of any preparation containing theophylline or aminophylline. Other formulations containing xanthine derivatives should not be given concurrently with Quibron elixir.

***Supplied:*** Each tablespoon of Quibron elixir (15 ml.) contains theophylline 150 mg. and glyceryl guaiacolate 90 mg. in a 15% hydro-alcoholic vehicle. Bottles of 8 fl. oz.

***References:*** (1) Schluger, J.; McGinn, J. T., and Hennessy, D. J.: Am. J. M. Sc. *233*:296-302 (March) 1957. (2) MacLaren, W. R.: California Med. *91*:278-282 (Nov.) 1959. (3) MacLaren, W. R.: Ann. Allergy *17*:729-739 (Sept.-Oct.) 1959. (4) Spielman, A. D.: Ann. Allergy *15*:270-276 (May-June) 1957. (5) Cass, L. J., and Frederick, W. S.: Am. Pract. & Digest Treat. *2*:844-851 (Oct.) 1951. (6) Schwartz, E.; Levin, L.; Leibowitz, H., and McGinn, J. T.: Am. Pract. & Digest Treat. *7*:585-588 (April) 1956. (7) Schiller, I. W., and Goldman, G.: Personal communication on file at the Mead Johnson Research Center.* (8) Levin, S. J., and Weisnagel, J.: Personal communication on file at the Mead Johnson Research Center.* (9) Puls, R. J., and Grater, W. C.: Current Therap. Res., in press (Nov.) 1961.

*These data are available to physicians on request.

67461

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*Symbol of service in medicine*

## Erythropoietin—a significant discovery in clinical hematology

A wealth of evidence now confirms the fact that red blood cell production is controlled by the hormone erythropoietin.[1-3] Demonstrated in human plasma,[4] erythropoietin has been shown to produce reticulocytosis,[1,5-7] increase utilization of the $Fe^{59}$ isotope, and increase erythrocyte precursors in marrow cultures.[3,8]

# ERYTHROPOIETIN FOUND TO CONTROL RED CELL FORMATION

**erythropoietin levels—new criteria in diagnosis of anemia** — Increased erythropoietin blood levels can be demonstrated in severe anemia and following the start of accelerated formation.[9] Soon thereafter, the effect of the higher levels appears as an increased erythroid marrow activity.[10] Since the hemopoietic marrow is capable of producing more red cells than normally required, many anemias may be due to inadequate erythropoietin levels—a result of subnormal production or excessive excretion.

**how does erythropoietin affect iron metabolism?** Absorption and utilization of iron are dependent upon the rate of bone marrow erythropoiesis which, in turn, is dependent upon erythropoietin levels.[11,12] Thus, the demand for iron created by accelerated erythropoiesis is satisfied by both increased gastrointestinal absorption and mobilization of storage iron. Inadequate erythropoietin levels would seemingly account for the frequently disappointing results with the use of iron alone in many of the anemias.

**can medication increase erythropoietin levels?** Cobalt has been shown to be strikingly effective in increasing the production of erythropoietin.[13,14] Cobalt-enhanced erythropoietin accelerates red cell production and improves iron utilization with a subsequent increase in hemoglobin and erythrocytes. The new concepts of the cause, diagnosis, and management of anemia may now be applied clinically on the sound basis of extensive studies published on RONCOVITE®—MF,* the therapeutic cobalt-iron hematinic.

(1) Gordon, A. S.: Physiol. Rev. **39**:1, 1959. (2) Erslev, A. J.: J. Lab. & Clin. Med. **50**:543, 1957. (3) Rosse, W. F., and Gurney, C. W.: J. Lab. & Clin. Med. **53**:446, 1959. (4) Gurney, C. W.; Goldwasser, E., and Pan, C.: J. Lab. & Clin. Med. **50**:534, 1957. (5) Rambach, W. A.; Alt, H. F., and Cooper, J. A. D.: Blood **12**:1101, 1957. (6) Gordon, A. S., **et al.**: Proc. Soc. Exp. Biol. & Med. **92**:598, 1956. (7) Erslev, A. J.: Blood **10**:954, 1955. (8) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood **13**:55, 1958. (9) Stohlman, F., Jr., and Brecher, G.: Proc. Soc. Exp. Biol. & Med. **100**:40, 1959. (10) Kraus, L. M., and Kraus, A. P.: Fed. Proc. **18**:1051, 1959. (11) Bothwell, T. H.; Pirzio-Biroli, G., and Finch, C. A.: J. Lab. & Clin. Med. **51**:24, 1958. (12) Beutler, E., and Buttenwieser, E.: J. Lab. & Clin. Med. **55**:274, 1960. (13) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science **125**:1085, 1957. (14) Murdock, H. R., Jr., and Klotz, L. J.: J. Am. Pharm. A. (Scient. Ed.) **48**:143, 1959.

*Cobalt chloride (cobalt as Co 3.7 mg.), 15 mg. ferrous sulfate exsiccated, 100 mg.

V-00361-R 104-R

LLOYD BROTHERS, INC.
Cincinnati, Ohio

CLINICAL PHARMACOLOGY and THERAPEUTICS

*volume* 2 *number* 6 **November-December 1961**

## Editorial

# Meaningful clinical classification of therapeutic responses to anticancer drugs

With the enormous increase in the clinical use of drugs to control the growth of cancer, it becomes essential to develop an acceptable and meaningful terminology to describe the indications and therapeutic effectiveness of each agent or procedure. The orderly presentation of information would serve as a guide to the practicing physician, and it would provide a common language to facilitate the collection and analysis of clinical experiences.

The clinical evaluation of a new drug in cancer has proved to be an extremely complex, tedious, and often elusive undertaking. In the research effort, the investigator is responsible for choosing a candidate agent, its dosage, and the route of administration, and for selecting appropriate patients for study. The care, wisdom, and perseverance which he contributes to the problem will determine the validity of his conclusions.

### Factors for consideration

In the absence of highly effective drugs with consistent effects on a variety of types of cancer and in order to arrive at meaningful evaluations, a number of important factors must be considered with respect to each patient admitted to the study.

***Site of origin.*** In the vast majority of patients, the presence of growing cancer and its site of origin are established by a pathologist. This information is mandatory before a patient is accepted for a clinical trial.

***Extent.*** It is necessary to determine, as accurately as possible, the mode of spread of the cancer, and the location of metastatic disease. This requires the systematic examination of each organ system, with appropriate biopsy, cytologic, biochemical, and roentgenologic studies, to determine the extent of clinically detectable cancer.

***Complicating problems.*** Organ and tissue functions can be deranged by the inroads of cancer or by the abnormal products of certain cancers. Examples of such occurences, some related to specific types of cancer, are neurologic disturbances, uremia, hepatic failure, pulmonary insufficiency, hemorrhage, impairment of immune response, and Cushing's disease. The aftereffects of treatment by surgical operation, radiotherapy, or chemotherapy may cause a variety of disturbances, such as functional

changes in the digestive tract, draining abscesses, anemia, hypopituitarism, or bone marrow depression, and each of these can dominate the clinical situation. The patient may be suffering from coincident or secondary conditions, such as cardiac failure, pneumonitis, hepatitis, or cirrhosis of the liver. These complications must be carefully analyzed, properly diagnosed, and corrected if possible prior to experimental chemotherapy. Regression of pulmonary shadows or improvement of hepatic status may be due to control of infectious processes, and serious errors can result from interpreting these as regression of cancer because of chemotherapy.

***Clinical course and response to previous therapy.*** A detailed case history is essential. The clinical duration and tempo in the progression of the disease are extremely important in interpreting therapeutic effects, and precise data on the response to previous chemotherapy at particular dose and toxicity levels make it possible to compare the effectiveness of different agents.

***Pattern of cancer.*** Within a histologically defined type, there is a great deal of variation in the course of nonresectable or recurrent disease. In some patients, the disease evolves rapidly, whereas in others, active disease can be present for many years without causing serious disability. Cancer, in individual patients, may show characteristic patterns of dissemination; some, for example, may metastasize predominantly to the lung, liver, or bone or remain locally confined to the site of origin. In several preliminary reports, we have described, in the great majority of patients with certain types of cancer, distinctive patterns for carcinoma of the lung[3] and of the large bowel,[4] melanoma, and ovarian cancer.[1] As detailed clinical experiences accumulate, it will be possible to define these patterns in statistical terms of survival period from the clinical onset of the disease or from the time of appearance of certain manifestations within the pattern. In carcinoma of the large bowel, for example, four patterns have been defined: (1) local extension alone, (2) hepatic metastasis, (3) intra-abdominal spreading, and (4) generalized metastases.[4] By the use of acceptable patterns, it may be possible to determine more precisely the situation in which the use of a drug may be expected to produce favorable and consistent effects.

***Stage of the disease.*** The stage of the disease prior to a therapeutic evaluation is obviously important in evaluating the response. Within the patterns of cancer, we have classified patients with nonresectable cancer into three clinical stages:

*Stage I.* The patient is asymptomatic, although cancer is present.

*Stage II.* There is progressive disease which is symptomatic but compensated in that the patient is able to do a moderate amount of work and care for his personal needs.

*Stage III.* There is progressive disease which is decompensated in that the patient has deteriorated to the point where hospitalization or constant medical assistance is necessary and he can no longer care for his own needs.

***Detection of a therapeutic response.*** Because of the many different forms and clinical manifestations of cancer, the criteria of response will vary not only with the specific type of cancer but with the individual patient. Methods are devised for objective measurements of tumor regression by means of palpation, by cytologic examinations, by comparative radioautographs, or by biochemical determination of enzymes, hormones, protein, or electrolytes in the blood or urine. In each patient selected for study, the measurable criteria that may be useful in demonstrating an antitumor response to therapy must be listed and these criteria periodically checked during the course of treatment. Each criterion is assessed and weighed separately in relation to the patient's clinical situation, for example, the correction of anemia after a severe pulmonary hemorrhage from lung cancer does not have the same significance as restoration of a normal hemoglobin level in acute leukemia. Despite extreme care,

many pitfalls exist in interpreting improvement in a measurable criterion of response as evidence of an anticancer effect.

Favorable subjective effects, such as relief of pain, dyspnea, or anorexia, are noteworthy, although these criteria by themselves are not adequate to establish the antitumor activity of a drug. In the presence of objective regression of cancer, subjective improvement acquires greater significance. Another criterion used in evaluating the response to therapy is the patient's performance status, which rates his level of useful activity and requirements for supportive measures.[2]

During the therapeutic trial, the introduction of other therapeutic measures immediately before, during, or after the administration of the new drug greatly complicates the interpretation of the clinical response. In brief, the investigator must select a suitable patient, order his management during the period of the study, and then accurately record the effects of treatment.

***Toxicity levels and categories of response.*** The total number of patients admitted to a clinical trial is recorded. In some cases, an adequate trial is not possible because the patient dies or complications intervene which interrupt or invalidate the study. The adequacy of the course of treatment should be defined in the patients who complete the course of treatment. In most cases, anticancer drugs are given to the point of toxicity in order to give the maximum opportunity for an anticancer effect, and this represents an adequate trial unless tumor regression and a satisfactory clinical response occur before any signs of toxicity appear. Drug toxicity often is a serious obstacle to the practical use of anticancer agents, and the level of toxicity should be estimated in relation to the therapeutic response. The limiting toxicologic effects are generally related to the cumulative action of the drug on certain proliferating tissues or organ functions, and for purposes of classification, four levels of toxicity are described.

1+ Slight but measurable signs.
2+ Moderate disturbances related to drug effect.
3+ Toxicity severe enough to be life threatening, although patient recovers.
4+ Toxicity either directly lethal or a proximate contributory cause of death.

A classification of the clinical response remains particularly difficult; some investigators report merely the unqualified term, response; others have listed objective or subjective improvement in any patient as a favorable response. Our group has classified the therapeutic effects of a drug, in terms of its anticancer activity, into three major categories of response. By anticancer effects, one means the ability of a drug to destroy or to control the growth of neoplastic cells. Transient regression of a mass or subjective improvement cannot be attributed to a specific or practical anticancer effect of a drug. To classify a response as of practical benefit to the patient, it is arbitrarily suggested that he sustain objective and subjective improvement for a minimum period of 1 month. Categorization of response does not exclude the recording of data which may be of scientific value, but it explicitly defines those results which are of real benefit to the patient.

### Categories of response

***Category 0. No clinically useful effect on course of disease.***

0-0 Disease progresses; no subjective benefit.
0-A* Disease progresses; subjective benefit without favorable objective changes.
0-B* Favorable objective changes without subjective benefit.
0-C Subjective benefit and favorable objective changes in measurable criteria, but of less than 1 month's duration; then the disease progresses.

*Categories apply as long as improvement from base line persists. Superscript is time in months of duration of response, e.g., 0-A$^4$ or I-B$^3$.

***Category I. Clinical benefit with favorable objective changes in all measurable criteria of disease.***

I-A* Distinct subjective benefit with favorable objective changes in all measurable criteria for 1 month or more.

I-B* Objective regression of all palpable or measurable neoplastic disease for 1 month or more in a relatively asymptomatic patient who is able to carry on his usual activities without undue difficulty. The observed tumor regression should be unequivocal, and it is suggested that all lesions be reduced at least 50 per cent in bulk. This category applies as long as the regression persists and ends if any lesion, old or new, recurs.

I-C Complete relief of symptoms, if any, and regression of all manifestations resulting from the active disease for 1 year or more. The relation to the frequency of therapy is not relevant if the disease does not recur between courses of therapy.

***Category II. Interruption or slowing in progression of disease without definite evidence of subjective or objective improvement.*** No criteria are presently available to classify this type of response. Statistical evidence of prolongation of survival time in specific patterns of cancer may some day be applicable.

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## Conclusion

Thus, a patient selected for chemotherapy will present a specific type, stage, and pattern of cancer, of known duration and responsiveness to previous treatment, with complications and unrelated diagnoses carefully identified. The criteria of evaluation are listed, the adequacy of the trial and level of toxicity determined, and the therapeutic response categorized. Data on individual patients are pooled with data obtained on patients with a similar type, stage, and pattern of the disease. These cumulative observations will result in response rate figures in the clinically useful category (I-A, B, C) and thus lead to the development of clear indications for the use of anticancer drugs in specific clinical situations.

### *References*

1. Golbey, R. B., Streeter, B., and Karnofsky, D. A.: Clinical observations on patterns of cancer, Acta Unio internat. contra cancrum **16**:1469-1960.
2. Karnofsky, D. A., and Burchenal, J. H.: The clinical evaluation of chemotherapeutic agents in cancer, *in* MacLeod, C. M., editor: Evaluation of chemotherapeutic agents, New York, 1949, Columbia University Press, pp. 191-205.
3. Karnofsky, D. A., Golbey, R. B., and Pool, J. L.: Preliminary studies on the natural history of lung cancer, Radiology **69**:477-488, 1957.
4. Young, C. W., and coauthors: Evaluation of therapeutic response of large bowel cancer to the fluorinated pyrimidines in relation to clinical patterns (abst.), Proc. Am. A. Cancer Res. **3**:164, 1960.

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# Effect of narcotic antagonists on the pupil diameter of nonaddicts

*The ability of the narcotic antagonists nalorphine and levallorphan to dilate the pupils of narcotic users and constrict the pupils of nonusers has led to their extensive employment in parole and probation work to detect narcotic use by former addicts. Since the test has been performed under field conditions without control studies, this investigation was done to determine the accuracy of measurement of pupil diameter by various methods and the effects of nalorphine and levallorphan on pupil diameter of normal subjects. It is concluded that even though there may be an appreciable variation in pupil diameter on consecutive readings before drug administration, both nalorphine and levallorphan generally cause a measurable miosis in subjects who do not use morphine or similar drugs. However, no single measurement of pupil size other than by photographic procedures should be considered to be absolutely reliable, especially if the pupil test alone is used as legal evidence for indicating use of narcotics.*

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Quantitative measurements of miosis caused by morphine and related drugs have been reported by Fraser and associates.[1] They measured pupil diameter by simultaneously photographing a centimeter rule and the eyes after the subjects had been in a darkened room 15 minutes. A stroboscopic light with a flash duration of 0.005 seconds permitted exposure of a photographic film without alteration of pupil size because of the light reflex. A 10 mg. amount of morphine decreased pupil diameter about 15 per cent for at least 6 hours, and larger doses produced even greater changes. Similar results were obtained with some morphine and methadone derivatives and with levorphan. Codeine and meperidine produced only minimal miosis. In 1956, as part of another study Fraser, Van Horn, and Isbell[2] showed that 3 to 10 mg. of nalorphine subcutaneously decreased pupil diameter by 10 to 15 per cent for 2 to 5 hours and that 10 mg. of nalorphine subcutaneously, given 1 ¾ hours after 30

This investigation was supported in part by contract No. 1137, Department of Justice, State of California.

Presented at the sixty-second annual meeting of the American Therapeutic Society, New York, N. Y., June 22-25, 1961.

Received for publication Aug. 3, 1961.

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mg. of morphine, subcutaneously, partially antagonized the miosis resulting from morphine.

Reports that nalorphine could mimic the abstinence syndrome in narcotic addicts[5] and that it might be used to diagnose narcotic addiction[3] led to its use by Terry and Braumoeller[4] for detecting narcotic users. The most consistent sign of narcotic use was dilation of the pupils after 3 mg. of nalorphine, and conversely, constriction of the pupils occurred in nonusers. Since their determinations of pupil size were made in the light-adapted eye with a simple card pupillometer (Fig. 1) and there was a certain percentage of subjects who showed no change of pupil size after nalorphine administration, it seemed desirable to examine the test under laboratory conditions.

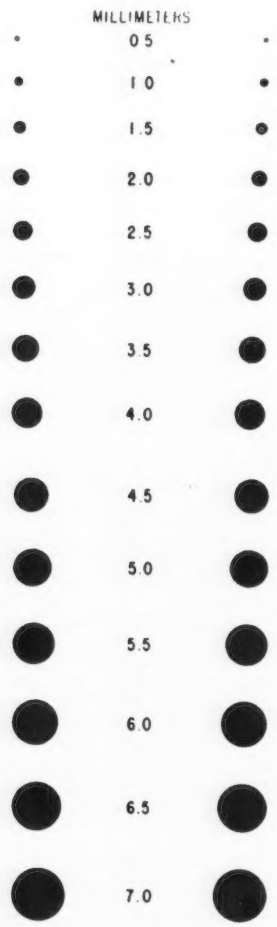


**Fig. 1.** The conventional card pupillometer used extensively in field testing for use of narcotics.

This report is concerned with (1) the accuracy of measurement of pupil diameter in the light-adapted eye, (2) the effect of 3 mg. nalorphine subcutaneously on the pupil size of volunteer nonaddicts, (3) a comparison of findings of two observers, and (4) the effect of 1 and 2 mg. of levallorphan subcutaneously on pupil size.

## Methods

For comparative purposes, the four instruments described below for measuring pupil diameter were used in one or more testing sessions.

1. A card pupillometer (Fig. 1) consisting of black disks of known diameter on a white background. It was held next to the subject's eye, and pupil size was determined by matching the pupil with a disk of the same size. This instrument has been widely employed in the detecting of narcotic use.[4]

2. A "hole" pupillometer constructed by drilling a series of holes between 2 and 6 mm. in diameter in a piece of Polaroid film (Fig. 2). The perforated card was held in front of the subject's eye, and the observer illuminated the pupil with an ophthalmoscope and determined pupil size by matching the pupil with one of the holes in the card. This device was developed to obviate the difficulty of identifying the border of pupils in the subjects with dark brown irises.

3. An ophthalmologic slit lamp with the light source dimmed by a Polaroid filter superimposed on a built-in gray filter was used to obtain greater accuracy in measurement. Pupils were measured directly with a 6 X eye piece equipped with a scale with 0.1 mm. increments.

4. A Speed Graphic camera equipped with a Polaroid Land camera back, a 105 mm. lens, a ring type flash unit, and a head holder were used for photographic measurements. A simultaneous photograph of the subject's right eye and a millimeter rule (Fig. 3) was taken on Polaroid Polapan 200 film and the pupil diameter determined from it with bow dividers.

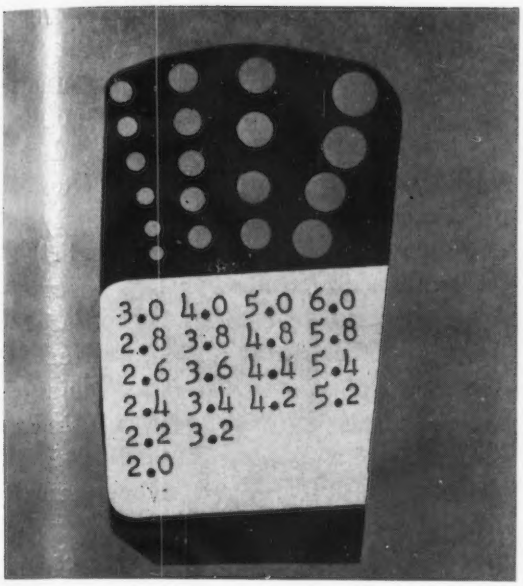


Fig. 2. The "hole" pupillometer developed to simplify determination of pupil size in dark brown eyes. Numbers refer to diameters in millimeters.

The subjects were volunteer medical and pharmacy students and laboratory personnel of both sexes. Testing sessions were held in the afternoon in a room provided with chairs for 10 to 15 subjects and lighted by two ceiling lights.

In the nalorphine studies, pupil size was determined with a card pupillometer by one observer and with a slit lamp by another observer. Subjects were called in turn, seated in a chair, and asked to steady their head by leaning against the wall and focus their eyes on a black spot on a 15 watt, 41 cm. daylight fluorescent bulb 2 M. away. The diameter of the right pupil was measured with a card pupillometer to 0.5 mm. by the first observer, who silently imparted the information to the recorder. The subject then moved to a chair facing a slit lamp, was positioned by the second observer, and was asked to focus his free eye on the wall about 1.5 M. away; the pupil diameter was measured, and the information was passed on to the recorder. Both measurements were repeated after 15 to 30 minutes, and after the final slit lamp reading, the second observer, using the double blind technique, gave each subject a subcutaneous injection in the upper arm of 0.6 ml. containing 3 mg. of nalorphine or 0.9 per cent sodium chloride. This dose of nalorphine was chosen because of its extensive use in the field for detecting narcotic users. Approximately 30 minutes later, the pupil diameter was again determined as described above, and each subject imparted his subjective reactions to the recorder.

Fig. 3. Photographic setup for measuring pupil size of suspected addicts.

When levallorphan was studied, pupil size was measured by three separate techniques. Readings with the card pupillometer were followed by measurements by a second observer who used a "hole" pupillometer. For this measurement, the subject continued to focus on the light used for the card reading, but the observer used an ophthalmoscope held about 18 inches from the subject's face to illuminate the pupil. By this method, even those pupils surrounded by very dark irises stood out as a spot of light which could easily be matched in size with the holes in the pupillometer. The subject next moved to a chair facing a camera, and a picture of his right eye and a millimeter rule was taken. Using the double blind technique, each subject was then given a subcutaneous injection in the upper arm of 1 ml. containing 1 or 2 mg. of levallorphan or 0.9 per cent sodium chloride. Approximately 30 minutes later, the readings were repeated, after which each subject related his subjective reactions to the recorder. If the subjects were nauseated or otherwise uncomfortable, they were observed in reclining chairs until they recovered; otherwise, they were released and asked to report back if an untoward reaction developed.

## Results

The studies were carried out on a total of 188 subjects in eleven testing sessions. In the initial nine sessions, pupil diameters were measured on 139 subjects, 73 of whom received nalorphine; the other 66 were given a saline placebo. On analysis of the data, it was obvious that the observers underwent a learning period, and since readings were more consistent after the third session, the data are accordingly presented in two parts (Figs. 4, 5, and 6).

***Variation in pupil diameter on successive readings.*** Fig. 4 shows the variation in diameter found in two separate readings made on the same pupil before injection. Here, learning by the observer using the card is apparent since only thirty-six (82 per cent) of his first forty-four determinations checked within 0.5 mm., whereas on the next 95 subjects, all readings checked within 0.5 mm. The observer using the slit lamp also had only thirty-six of his first forty-four determinations check within 0.5 mm., but on the next 95 subjects, eighty-six (90 per cent) checked within 0.5 mm. Both methods indicate that variations in pupil size of ± 0.5 mm. will occur frequently on consecutive readings, and occasionally even greater variations may be seen. On the other hand, fifty-seven (61 per cent) of the measurements on the pupils of 95 subjects made with the slit lamp showed a variation of ± 0.2 mm. or less.

***Effect of a saline placebo on pupil diameter.*** Again, as shown in Fig. 5, after the learning period, results with the card were less variable than with the slit lamp. In this and the following figures, changes in pupil

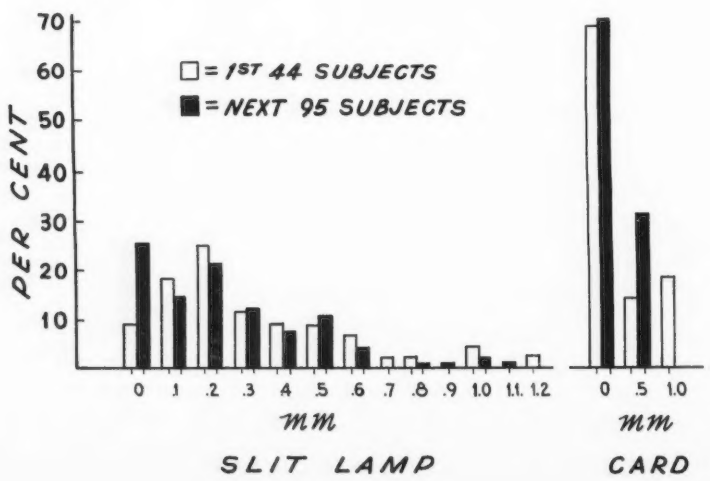


**Fig. 4.** Variation in pupil diameter on two consecutive readings about 15 minutes apart.

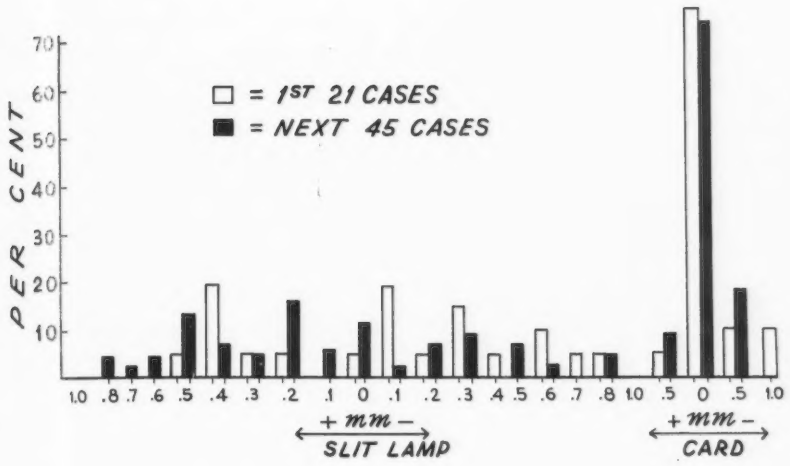


**Fig. 5.** Effect of saline placebo on pupil diameter.

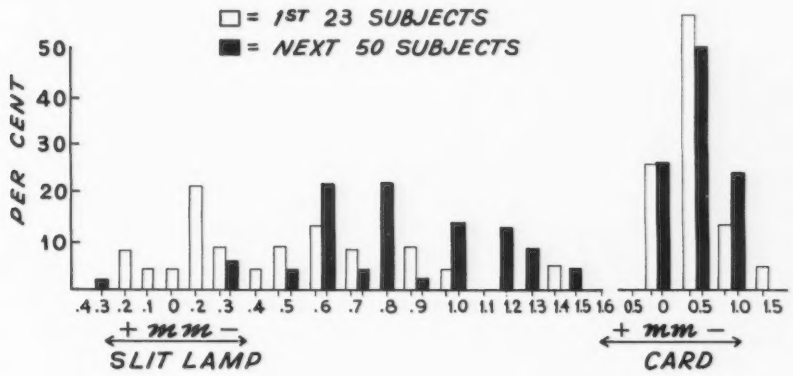


Fig. 6. Effect of nalorphine on pupil diameter.

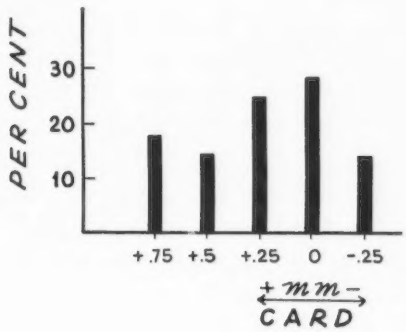


**Fig. 7.** Variations of pupil diameter readings made by observer H. E. from those made by observer T. F.

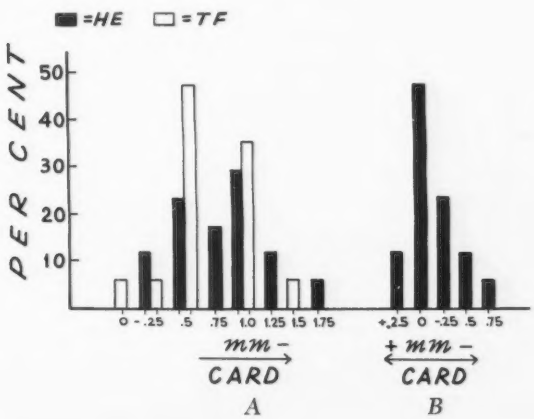


Fig. 8. *A*, Comparison of results obtained by observer H. E. with those of observer T. F. in subjects who had received 3 mg. of nalorphine subcutaneously. *B*, Deviation of readings by H. E. from those made by T. F.

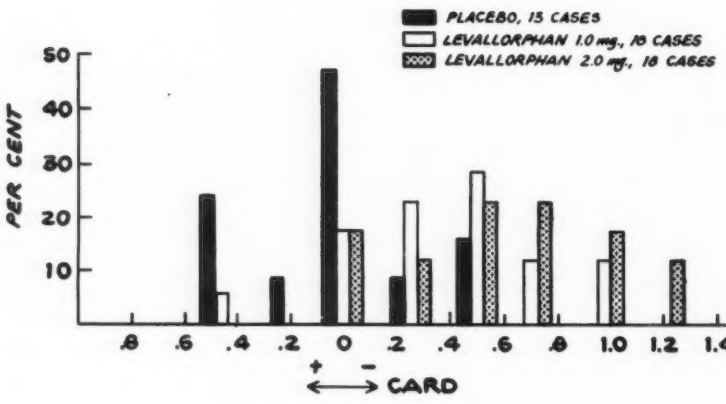


**Fig. 9.** Changes in pupil diameter after levallorphan or placebo reported by observer T. F. using the card pupillometer.

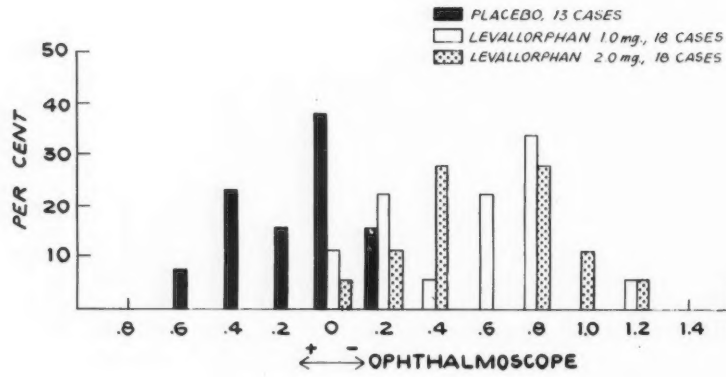


**Fig. 10.** Changes in pupil diameter after levallorphan or placebo reported by observer H. E. using the hole pupillometer and ophthalmoscope.

size are shown as an increase or a decrease (plus or minus). Thirty-three of forty-five measurements (73 per cent) showed no change, and the remaining twelve (27 per cent) varied between ± 0.5 mm. With the slit lamp, pupil diameter varied between ± 0.8 mm. Thirty-seven of forty-five measurements (82 per cent) were between ± 0.5 mm.

***Effect of nalorphine on pupil diameter.*** The effect of 3 mg. of nalorphine subcutaneously is shown in Fig. 6. The observer using the card reported a decrease in pupil diameter of 0.5 mm. or more in fifty-four of seventy-three measurements (73 per cent). However, nineteen (26 per cent) of his measurements demonstrated no change in pupil diameter. Both the learning and subsequent sessions are included since there was no apparent difference between them. Not one case of pupillary dilation was noted. The observer who used the slit lamp found a variation of ± 0.2 mm. in nine of twenty-three measurements (39 per cent) made during the learning period, but subsequently, forty-nine of fifty measurements (98 per cent) showed a decrease of pupil diameter of 0.3 mm. or more. The single subject whose pupil showed a dilation of 0.3 mm. on a recheck showed a constriction of 1 mm. The results indicate that with a sensitive instrument for estimating pupil diameter, 3 mg. of nalorphine subcutaneously will generally produce measurable miosis in subjects who do not use narcotics.

***Comparison of results of two observers using card pupillometer.*** In another experiment with 28 subjects, the measurements of two observers made with the card pupillometer were compared. Pupil diameters were estimated to 0.25 mm. Fig. 7 shows that observer H. E. tended to report larger control pupil diameters than did observer T. F. However, as shown in Fig. 8, both observers agreed closely in their es-

timates of miosis in 17 subjects who had received nalorphine, allowing for the fact that H. E. reported finer incremental changes than T. F. Observer T. F., who reported 26 per cent as no change in the previous series, reported no change in only 1 subject (6 per cent) in the present series, and H. E. reported miosis of at least 0.25 mm. in all 17 subjects. Even though T. F. tended to report changes in increments of 0.5 mm. and H. E. estimated at the 0.25 mm. interval, their estimates of the degree of miosis caused by nalorphine were comparable as indicated by the fact that in 14 of the 17 subjects (82 per cent), the two observers agreed within ± 0.25 mm.

***Effect of levallorphan on pupil diameter.*** In two additional testing sessions, measurements were made on 49 subjects; 18 received 1 mg. of levallorphan, 18 received 2 mg. of the drug, and 13 were given the saline placebo.

Fig. 9 shows the changes in pupil size resulting from levallorphan and placebo as determined by observer T. F. with the card pupillometer. The expected random size changes occurred after the placebo, but after 1 mg. of levallorphan, the pupil diameter decreased by 0.25 mm. or more in 14 of the 18 subjects (78 per cent). No change was reported in 3 subjects (17 per cent), and a dilation of 0.5 mm. was reported in 1 subject (6 per cent). (This subject showed pupillary constriction by the other methods of measurement). After 2 mg., pupil diameter decreased by 0.25 mm. or more in 15 of the 18 subjects (83 per cent), and no change was reported in the other 3 cases (17 per cent). A 2 mg. amount did not appear markedly to increase miosis.

Fig. 10 shows the changes in pupil size in the same subjects, as determined by observer H. E. with the hole pupillometer and ophthalmoscope. Again, random changes followed the placebo, but after 1 mg. of levallorphan, pupil diameter decreased 0.2 mm. or more in 16 of the 18 subjects (89 per cent) and after 2 mg. in 17 of the 18 subjects (94 per cent).

Fig. 11 shows the changes in pupil size determined photographically. As usual, use of the placebo resulted in random changes, and after 1 mg. of levallorphan, pupil diameter decreased 0.2 mm. or more in 12 of 15 subjects (80 per cent). After 2 mg., pupil size decreased 0.3 mm. or more in all 13 subjects. There are fewer subjects in this category because the camera was not used in the first session.

The incidence of side effects resulting from nalorphine was unexpectedly high considering the size of the dose used. Therefore, the subjects were not permitted to tell how they felt until all pupil measurements were completed, in order to avoid influencing the observers. Of the 90 subjects receiving nalorphine, 81 (90 per cent) reported effects, mostly central or parasympathetic in nature, which could be attributed to the drug. In contrast, only 11

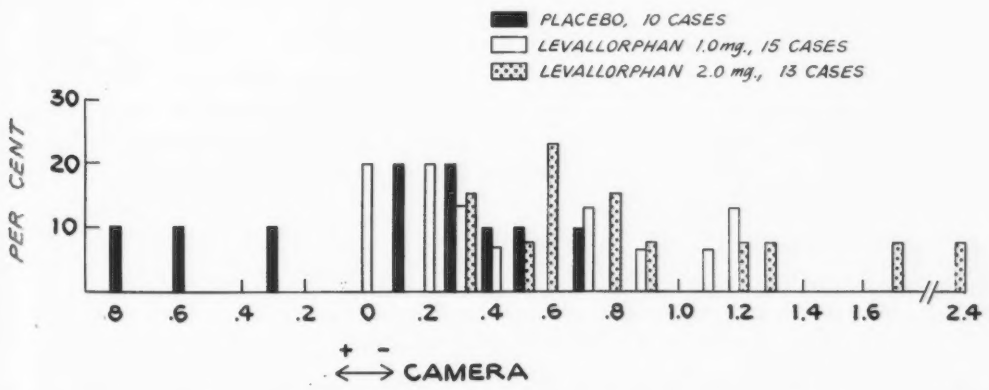


Fig. 11. Changes in pupil diameter after levallorphan or placebo obtained by measuring the pupils in photographs of the subjects' right eye.

**Table I.** *Subjective effects reported by subjects 30 minutes after injection of nalorphine or placebo*

| Effect | Nalorphine | | Placebo | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Dizziness | 48 | 53.3 | 3 | 3.9 |
| Lightheadedness | 20 | 22.2 | 2 | 2.6 |
| Tiredness | 13 | 14.4 | 2 | 2.6 |
| Peripheral vascular effects | 13 | 14.4 | 1 | 1.3 |
| Ataxia | 8 | 8.9 | 1 | 1.3 |
| Sweating | 8 | 8.9 | | |
| Nausea | 7 | 7.8 | | |
| Visual effects | 4 | 4.4 | | |
| Alcohol-like action | 3 | 3.3 | | |
| Delayed central nervous system effects, nausea | 2 | 2.2 | | |
| Euphoria | 1 | 1.1 | | |
| Headache | 1 | 1.1 | 1 | 1.3 |
| Vomiting | 1 | 1.1 | | |
| Salivation | 1 | 1.1 | | |
| "Medicated" feeling | 1 | 1.1 | | |
| Nervousness | | | 1 | 1.3 |
| None | 9 | 10.0 | 67 | 87.0 |

of the 77 subjects (13 per cent) who were given the saline placebo reported subjective effects, which were uniformly mild. Subjective effects are listed in Table I in order of frequency of incidence in subjects receiving nalorphine. There was no apparent relationship between severity of untoward effects and change in pupil size. Subjective reactions reported by the subjects who received levallorphan were similar to those reported after nalorphine, with perhaps a greater incidence of delayed gastrointestinal and central nervous system effects at the 2 mg. dose level. It would be necessary, however, to increase the size of the series to make a valid comparison. Those delayed effects which were fairly severe occurred when the subjects were allowed to ambulate after the 30 minute observation period and usually included nausea and dizziness severe enough to force the individual to lie down for 30 to 60 minutes. The incidence of untoward effects in our subjects, none of whom were narcotic users, was, as might be expected, higher than that reported by practitioners using the test on known narcotic users.

## Discussion

This study indicates that even though there may be an appreciable variation in pupil diameter on consecutive control readings, nalorphine and levallorphan generally cause a measurable miosis in subjects who do not use morphine or similar drugs. In only two isolated instances was pupillary dilation noted. In the case with nalorphine and the slit lamp, a recheck on the same individual failed to confirm the original observation, and although a recheck of the subject who showed dilation by the card measurement after levallorphan was not done, he showed miosis by two other methods of measurement. A 3 mg. dose of nalorphine subcutaneously caused miosis in 49 of 50 subjects when measurements were made by the reasonably sensitive slit lamp technique; and 2 mg. of levallorphan caused miosis in all of 13 subjects when pupil size was determined photographically. With the less sensitive pupillometer techniques, 1 mg. of levallorphan gave approximately as good results as 3 mg. of nalorphine, but since 3 of 15 subjects given 1 mg. of levallorphan showed no change by the photographic technique, further work will be required to determine the minimal dose of levallorphan equivalent to 3 mg. of nalorphine. Tentatively, it appears that this dose is between 1 and 2 mg.

With the simple pupillometers, it may be expected that some subjects with slight miosis will be reported as showing no change in pupil size after an effective dose of either nalorphine or levallorphan. The actual percentage will vary with the skill and experience of the observer, but it is obvious that a more sensitive method of measurement is desirable. Thus, after 3 mg. of nalorphine, pupils in 19 per cent of 73 subjects showed no change in diameter when measured with the card, but when in 50 of the same subjects pupils were measured with the slit lamp, only 2 per cent showed no decrease in size. The slit lamp

provides adequate sensitivity, but photographic techniques, besides being sensitive, are more accurate and provide a permanent record of the test results.

In conclusion, our findings support the premise that morphine antagonists are highly useful to confirm a subject's contention that he is not using narcotics, since doses which do not produce a high incidence of serious untoward effects produce miosis in most nonusers. The simple pupillometers may be adequate in the hands of trained observers, since the usual decrease in pupil diameter amounts to 0.5 mm. or more, but more accurate measurements such as can be made from photographs should reduce the number of equivocal or no change reactions reported. The fact that in two instances an apparent human error of measurement occurred with the card pupillometer and the slit lamp indicates that no single measurement of pupil size other than by photographic procedures should be conceded to be absolutely reliable, especially if the pupil test alone is used as legal evidence for indicating use of narcotics.

The nalorphine and levallorphan used in these studies were kindly supplied by Merck Sharp & Dohme, West Point, Pa., and Roche Laboratories, Nutley, N. J., respectively.

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# Effects in normal man of α-methyltryptamine and α-ethyltryptamine

*DL-α-Methyltryptamine methyl sulfate in oral doses of 20 mg. and DL-α-ethyltryptamine acetate in oral doses of 150 mg. were compared objectively and subjectively in a group of trained, normal human volunteers. Blood pressure, pulse rate, pupil diameter, oral temperature, and grip strength were recorded hourly. Subjective effects were recorded 3 and 24 hours after administration of the drugs.*

*A significant decrease in heart rate occurred 2 hours after α-ethyltryptamine. Significant rises in systolic and diastolic blood pressure occurred 3 hours after α-methyltryptamine. There also were significant increases in pupil diameter after each drug.*

*The subjective effects were similar in many respects, but there were important differences. The onset of action was rapid for α-ethyltryptamine and slow for α-methyltryptamine; duration of action was longer for the latter than for the former. The most common effect, reported by 8 of the 11 subjects taking α-ethyltryptamine, was a feeling of being elated or intoxicated. The most common effects reported by those who took α-methyltryptamine were nervous tension and restlessness not unlike those produced by 50 to 60 μg of lysergic acid diethylamide.*

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Tryptamine and 5-hydroxytryptamine are two metabolic amines formed in the body by decarboxylation. A study of the DL-α-methyl and DL-α-ethyl congeners of tryptamine has shown each of these to be active monamine oxidase inhibitors in vitro. Recent investigations at The Upjohn Company* and by Greig, Walk, and Gibbons[2] indicate that the inhibiting actions of the two derivatives do not differ greatly.

## Pharmacologic properties

***α-Methyltryptamine.*** Oral $LD_{50}$ in the rat is given by Sandoz, Inc.,† as 138 ± 25 mg. per kilogram (weight, age, and strain not

This study was supported in part by grants M-875 and MY-4229 from the National Institute of Mental Health, U. S. Public Health Service, and by a grant from the Geschickter Fund for Medical Research, Inc.

Received for publication June 13, 1961.

*Alan B. Varley: Personal communication, April, 1961.

†A. Cerletti: Via personal communication from R. Bircher, September, 1959.

Table I. *Number of subjects who reported each effect of α-methyltryptamine and α-ethyltryptamine 24 hours after administration*

| Effect | α-Methyltryptamine methyl sulfate, 20 mg. (12 subjects total) | α-Ethyltryptamine acetate, 150 mg. (11 subjects total) |
|---|---|---|
| Visual flashes | 1 | 2 |
| Blurred vision | 3 | 3 |
| Exhilaration and/or intoxication | 3 | 8 |
| Dizziness | 3 | 2 |
| Muscle cramps or tightness | 4 | 3 |
| Numbness | 2 | 1 |
| Nervous tension | 7 | 2 |
| Afternoon lethargy or sedation | 1 | 5 |
| Restlessness, inability to relax in afternoon | 7 | 0 |
| Headache | 3 | 2 |
| Analgesia | 2 | 0 |
| Loss of appetite and/or slight nausea | 5 | 6 |
| Hangover | 4 | 4 |
| Lysergic acid diethylamide simulation | 1 | 0 |
| Similar to lysergic acid diethylamide | 7 | 1 |
| Lysergic acid diethylamide plus something more | 1 | 1 |

specified); the same source indicates mydriasis and pressor effect in the cat with rapid tachyphylaxia. However, The Upjohn Company* finds $LD_{50}$ in the rat to be 22.4 ± 4.4 mg. per kilogram.

***α-Ethyltryptamine.*** Oral $LD_{50}$ in the rat is 48 ± 11 mg. per kilogram (The Upjohn Company*), and intraperitoneal $LD_{50}$ in the mouse is 72.5 ± 16 mg. per kilogram. The compound is nontoxic at 10 mg. per kilogram per day orally for 4 weeks in rats and at a dosage of 3 mg. per kilogram per day orally for 21 days in dogs; intravenous injection produces a slight pressor effect in the dog. The relative toxicities of the α-ethyltryptamine and α-methyltryptamine, therefore, are not entirely clear at present, but they are evidently of the same order of magnitude.

## Methods

***Selection of subjects.*** As in similar studies,[1] the subjects were inmates of the U. S. Penitentiary, Atlanta, who volunteered for the study. After careful screening, the subjects were introduced to the pharmacologic effects of D-lysergic acid diethylamide. During a 4-week period, successive oral doses of 25, 50, 75, and 100 μg were administered at 1 week intervals. In this way, each subject became fully familiar with the effects of the drug both qualitatively and quantitatively.[1] They also were trained to know that only an unbiased opinion about their subjective effects was wanted and that their status on the project was not dependent on giving "right answers." Each experimental procedure included active and inert blanks, and the subjects were also given doses of lysergic acid diethylamide from time to time. This was intended to help them keep in mind their scales of subjective effects so that they would be, insofar as possible, neither "placebo reactors" nor unduly skeptical. It served at least to keep them alert at all times to the question of whether they received an active drug or a blank. For participating, each man was given $3 for each week on the project and 3 days' "good time," i.e., credit toward conditional release, for each month on the project. In all, there were 16 subjects.

***Assay of new compounds.*** It is our usual policy to begin the testing of a new compound with a trivial dose in 1 individual only. This is gradually increased until a

*Alan B. Varley: Personal communication, April, 1961.

**Table II.** *Representative 24 hour reports*

| *Time* | *Subjects' description of effects* |
|---|---|
| *Subject K: α-methyltryptamine, 20 mg. oral dose* | |
| 8:00 A.M. | Reported to project after good night's sleep |
| 8:30 | Received drug |
| 11:30 | For first 3 hours, no effects; thought I'd had a blank |
| 12:30 P.M. | Becoming physically uncomfortable, muscles tense, nervous, irritable, stomach slightly unsettled |
| 2:30 | Very restless; can't sleep; must be LSD, but this delayed reaction is something new to me; lots of nervous tension, stiff neck, blurry vision, loss of depth perception; would equate this to 50 γ LSD-25 in case LSD was not given |
| 5:00 | Excessive dilation of pupils about 8 mm., but no resulting distortion or fuzziness |
| 8:00 | Judgment impaired to some extent, probably through sheer fatigue; I feel completely washed out and spent physically |
| Next day | If LSD, then strong dosage, since effects never completely receded before going to sleep (midnight); the next morning considerably "hung over," feeling run down, and mentally sluggish |
| *Subject H: α-ethyltryptamine, 150 mg. oral dose* | |
| 8:30 A.M. | Received drug, ate no breakfast |
| 9:00 | Felt the drug right away, felt dizzy, intoxicated; things are picking up |
| 9:30 | At first check felt fine, stimulated; thought my eyes were going out of focus, but they settled down |
| 10:30 | Still riding high; can't figure if I'm nervous and tense or just intoxicated |
| 11:30 | Ate no lunch, feel good, thought the doctor had already left; talking a lot, in fact at one time wouldn't answer anyone in plain English, had to spout gibberish at them |
| 12:30 P.M. | Still talking gibberish, but starting to come down off my high |
| 1:30 | Lethargy is starting to set in |
| 3:00 | Drowsy, stomach feels jittery; would like to sleep |
| 8:00 | Throat is sore from talking too much, slight headache |
| 11:00 | Going to be *tired* and let down |
| Next day | Awoke feeling fair, little used up; throat feels very tired |

predetermined level is reached or until effects are noticed. DL-α-Ethyltryptamine acetate was given orally in an initial dose of 30 mg. This was increased in increments of 15 mg. at weekly intervals to a level of 150 mg. At this dose, the drug effects were definite. Following a Latin square design with crossovers, 11 subjects received this dosage, the remainder receiving in all instances only lactose placebos. The drug was given at 8:30 A.M. after baseline observations of blood pressure, pulse rate, oral temperature, and grip strength had been made. These measurements were repeated at hourly intervals after medication. At the end of the test period, the subjects were asked nondirectively to describe the effects of the medication. The physician who made the inquiries did not know at the time what the subjects had been given. The subjects also made 24 hour reports after administration. The same procedure was followed for the testing of DL-α-methyltryptamine methyl sulfate (IT-290), except that the first dose was 10 mg. and the largest dose 20 mg. Twelve subjects received the 20 mg. dose of active compound in this study.

## Results

***Subjective observations.*** Table I shows the range of subjective effects produced by the two compounds as abstracted from the 24 hour reports. As reported by our subjects, the onset of action of α-methyltryptamine is slow after oral administration, becoming noticeable only after 3 to 4 hours. The duration of action was long, usually 12 to 24 hours, with 2 subjects reporting a duration of 2 days. Ten of the 12 reported unpleasant feelings: nervous tension, irrita-

bility, restlessness, and inability to relax and sleep during the afternoon. Visual effects were not pronounced, but 3 reported difficulty in focusing, 1 a few flashes of light. Two subjects, 1 who arrived for the experiment with a headache, the other with a headache and a toothache, reported an analgesic effect lasting about 3 hours. In general, the subjects did not like the drug, expressed feelings of discomfort, and likened the effects to a long-lasting lysergic acid diethylamide–like compound.

α-Ethyltryptamine, on the other hand, was characterized by a more rapid onset of action (30 to 90 minutes). Eight of the 11 subjects reported feelings of intoxication. Two stated that they felt "stimulated." One reported no effect other than feeling "hot and itchy." Five noted an afternoon lethargy, letdown, or sedation. Only 1 reported that he slept poorly, and that because of a headache. Four reported a hangover the next day. But for the most part the effects were short (2 to 6 hours) or moderate (6 to 12 hours) in duration. Six subjects reported loss of appetite and/or slight nausea. Muscle effects consisted of cramps or tenseness and weakness or numbness. Three reported visual disturbances; these consisted of blurred vision or a few flashes of light. Only 2 equated the drug to something like lysergic acid diethylamide. The most prominent effect, therefore, of 150 mg. of α-ethyltryptamine is a feeling of intoxication accompanied by loss of appetite. This intoxicated or elated feeling lasts 4 to 5 hours and gives way to lethargy, sedation, or a letdown feeling.

Table II gives two representative 24 hour reports in full.

***Objective observations.*** Table III shows mean blood pressures, heart rates, and, in the case of α-ethyltryptamine only, grip strengths, as recorded at hourly intervals.

α-Methyltryptamine produced an increase in systolic and diastolic blood pressure 3 hours after administration. α-Ethyltryptamine caused slowing of the heart rate at 2 hours, with return to control value at 3 hours. The matched controls, who received only blanks during the same experimental periods, showed no significant changes in any of the variables.

It is to be noted that delayed physiologic actions may have been missed, since recordings were not made later than 3 hours after dosage.

Pupil diameter data were set in a matrix of "larger than," "same as," or "smaller than" control values. The chi square test yielded the following results: for α-methyltryptamine 4.58, which with $df=3$ gives $P < 0.05$; for α-ethyltryptamine 17.41, which with $df=3$ gives $P < 0.01$. In both cases, the pupil diameters were increased.

## Discussion

These results strongly suggest that monamine oxidase inhibition as determined in vitro or even in vivo is not a reliable indicator that a compound will have useful drug action. It might seem that inhibition

**Table III.** *Physiologic observations after dosage with α-methyltryptamine and α-ethyltryptamine*

| Compound | Observation | Time | | | |
|---|---|---|---|---|---|
| | | Control | 1 hr. | 2 hr. | 3 hr. |
| α-Methyltryptamine | Systolic blood pressure (mean mm. Hg) | 118.7 | 118.8 | 118.9 | 124.4* |
| | Diastolic blood pressure (mean mm. Hg) | 70.6 | 71.8 | 74.6 | 76.7* |
| | Heart rate (per minute) | 80.0 | 78.3 | 80.7 | 84.4 |
| α-Ethyltryptamine | Systolic blood pressure | 117.7 | 113.2 | 119.1 | 120.9 |
| | Diastolic blood pressure | 70.5 | 69.1 | 70.9 | 70.9 |
| | Heart rate | 77.0 | 73.0 | 69.0* | 75.0 |
| | Grip strength (Kg.) | 48.0 | 49.0 | 46.0 | 45.0 |

*Differs from control, $P < 0.05$.

of the enzyme that destroys some amines in part should result in gradually developing central nervous system stimulation because of an inferred build-up of epinephrine and norepinephrine in the central nervous system. However, these two compounds, and probably others with monamine oxidase inhibitory activity, have variable stimulant, depressant, or confusional effects in man.

α-Methyltryptamine and α-ethyltryptamine, since they are structurally very similar and are monamine oxidase inhibitors in vitro, would be expected to have comparable action when administered orally to human subjects. Many of the effects listed by the subjects are similar, but the differences are more striking. α-Methyltryptamine produces a delayed effect in man after an oral dose of 15 mg., while α-ethyltryptamine produces an immediate feeling of intoxication when given in an oral dose of 150 mg. and the effects have mostly subsided in 5 to 6 hours.

It is apparent from the 24 hour reports that visual effects are similar, consisting of blurred vision or difficulty in focusing and a few flashes of light similar to those with lysergic acid diethylamide. Both drugs produce dilation of the pupils, as does lysergic acid diethylamide. Other subjective effects common to both compounds and reported with approximately equal frequency are muscle cramps or tightness, headache, loss of appetite and/or slight nausea, dizziness, and numbness. Although the duration of action of α-ethyltryptamine is shorter, 4 subjects in each case complained of a hangover the day after the doses were administered.

The main differences reported were feelings of exhilaration or intoxication, apparently not unpleasant with α-ethyltryptamine, and feelings of tenseness, restlessness, and generalized malaise with α-methyltryptamine. α-Methyltryptamine at a dose of 20 mg. was likened to lysergic acid diethylamide by 9 of the 12 subjects, while α-ethyltryptamine at a dose of 150 mg. was likened to it only by 2 subjects, who felt however that the apprehension and visual effects of lysergic acid diethylamide intoxication were lacking.

The delayed action of α-methyltryptamine suggests that a metabolic product rather than the compound itself might be the active agent.

## Conclusion

α-Ethyltryptamine appears to be much less potent than α-methyltryptamine. The effects are similar in several respects but differ markedly in others. α-Ethyltryptamine even in large doses is less psychotomimetic, since the subjects who compared it to lysergic acid diethylamide volunteered that it did not produce the apprehension or the same kind of visual effects. Nine of the 12 subjects who received α-methyltryptamine likened its effects to those of D-lysergic acid diethylamide.

Neither of these compounds, under our conditions of testing, is a reliable central nervous system stimulant.

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# Clinical evaluation of phendimetrazine bitartrate

*Clinical investigation of a phenmetrazine congener, phendimetrazine, was performed by using double blind controls. Of 50 obese patients who participated, 36 completed one adequate course of active drug or placebo and 20 completed both phases of the study. The average total weight lost and the average weight lost weekly by patients who received phendimetrazine were about 20 times as much as those of patients who received placebo. Comparison of the two groups showed no significant difference in undesirable effects. The over-all incidence of subjective complaints or minor toxic reactions was negligible, and examination including pulse, blood pressure, blood count, and urinalysis showed no evidence of major change.*

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Phendimetrazine bitartrate* (D-2-phenyl-3,4-dimethylmorpholine bitartrate) differs from phenmetrazine in that it is a D-isomer and has a methyl group. No information was available on clinical use in humans, but there had been demonstrated in animal experiments[6] an anorexiant effect similar to that of phenmetrazine, which has been extensively investigated and is in use.[5] Toxic reactions and the central-stimulating sympathomimetic properties were also similar, but in the laboratory animal, there were fewer undesirable effects and, in large intravenous doses, less change in heart rate, blood pressure, and respiration.

The following study was designed to examine the anorectic properties of the drug in man.

Received for publication July 3, 1961.
*Plegine.

## Material and method

Without any attempt at selection, all obese patients referred to the Endocrine Clinic were included in the study. The routine work-up consisted of a regular medical history, physical examination, blood count, urinalysis, and blood cholesterol, basal metabolism, and $I^{131}$ tracer determinations. Return visits were at 2 week intervals; on these occasions, weight, blood pressure, and pulse were recorded and the patients were questioned and examined for subjective and objective reactions. From time to time, the laboratory tests were repeated.

Two identical tablets, numbers 1 and 2, representing either placebo or 35 mg. of phendimetrazine bitartrate, were used. The identity of the two tablets was retained by the manufacturer in a code. During the initial interview, each patient was given a

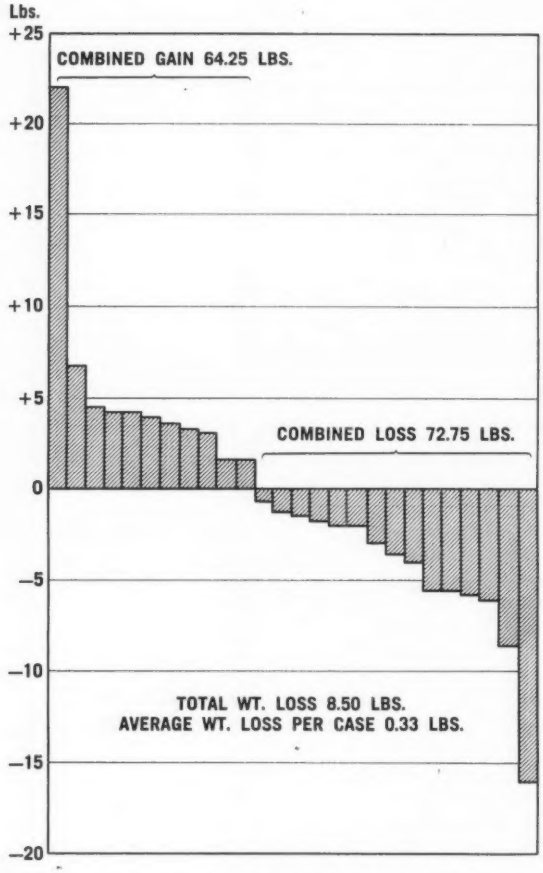


**Fig. 1.** Weight changes with placebo (26 patients).

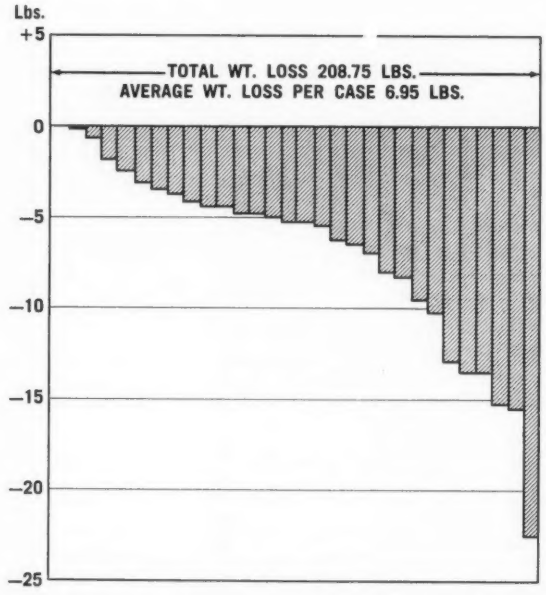


**Fig. 2.** Weight changes with phendimetrazine (30 patients).

verbal description and a handwritten 1,100 calorie specimen diet; the subjects were alternately given tablet 1 or 2, one tablet three times daily ½ hour before meals. No further emphasis was placed on diet. After 3 months on one medication, administration was changed to the other tablet without informing the patient. Fifty obese individuals were finally enrolled in the study. Upon its completion, we were informed that tablet 1 was the placebo and tablet 2 phendimetrazine.

### Results

At the beginning of the study, there was a flurry of viral infections with gastrointestinal symptoms in our clinical population which led to a number of drop-outs, but 36 of 50 patients remained under observation; of these, 20 completed both phases of the study in a 6 month period. All of the latter lost weight with phendimetrazine, while some gained and some lost with the placebo. For the entire group, there were 26 courses of the placebo, with 15 subjects losing and 11 gaining weight; the average weight loss with placebo was 0.33 pound, or 0.025 pound per week. There were 30 courses of phendimetrazine, and 29 patients lost weight and 1 remained the same; the average weight loss with phendimetrazine was 6.96 pounds, or 0.54 pound per week, more than 20 times that with the placebo. The results are summarized in Table I and diagramed in Figs. 1 and 2.

A review of the 14 patients who dropped out revealed that 8 were taking placebo and 6 were taking phendimetrazine at the time. There were no significant differences in the minor toxic effects. With tablet 1 there were five complaints and with tablet 2 six. Almost all complaints were of gastrointestinal upset, but there were at least one mention of nervousness with each and one of metallic taste in the mouth with the active drug. Minor toxic effects, then, were negligible, and on repeated examination, no severe toxicity or significant change was noted.

**Table I.** *Summary of study*

| | *Placebo (tablet 1)* | | | | *Phendimetrazine (tablet 2)* | | | |
|---|---|---|---|---|---|---|---|---|
| *Patient* | *Weeks* | *Start* | *Finish* | *Change* | *Weeks* | *Start* | *Finish* | *Change* |
| 1 | 14 | 193.00 | 191.25 | − 1.75 | 14 | 201.00 | 193.00 | − 8.00 |
| 2 | 15 | 168.50 | 171.50 | + 3.00 | 15 | 173.75 | 168.50 | − 5.25 |
| 20 | 17 | 146.50 | 141.00 | − 5.50 | | | | |
| 3 | 13 | 147.50 | 146.75 | − 0.75 | 14 | 152.00 | 147.50 | − 4.50 |
| 26 | | | | | 5 | 292.00 | 279.00 | −13.00 |
| 4 | 14 | 140.50 | 137.50 | − 3.00 | 14 | 137.50 | 129.25 | − 8.25 |
| 27 | | | | | 20 | 210.25 | 204.75 | − 5.50 |
| 5 | 13 | 305.50 | 309.75 | + 4.25 | 14 | 309.75 | 305.00 | − 4.75 |
| 6 | 14 | 144.50 | 148.00 | + 3.50 | 14 | 148.00 | 144.25 | − 3.75 |
| 21 | 14 | 250.50 | 246.50 | − 4.00 | | | | |
| 7 | 15 | 205.00 | 199.50 | − 5.50 | 12 | 199.50 | 192.50 | − 7.00 |
| 8 | 5 | 226.25 | 230.50 | + 4.25 | 13 | 230.25 | 226.00 | − 4.25 |
| 9 | 14 | 167.00 | 151.00 | −16.00 | 14 | 151.00 | 144.50 | − 6.50 |
| 22 | 12 | 204.50 | 202.50 | − 2.00 | | | | |
| 10 | 12 | 189.25 | 180.75 | − 8.50 | 12 | 180.75 | 176.00 | − 4.75 |
| 28 | | | | | 13 | 225.75 | 223.75 | − 2.00 |
| 11 | 8 | 160.50 | 162.00 | + 1.50 | 26 | 163.00 | 160.50 | − 2.50 |
| 36 | 14 | 240.50 | 262.50 | +22.00 | 15 | 250.75 | 240.50 | −10.25 |
| 12 | 14 | 234.50 | 237.75 | + 3.25 | 14 | 237.75 | 237.50 | − 0.25 |
| 23 | 14 | 196.25 | 194.75 | − 1.50 | | | | |
| 13 | 13 | 182.00 | 183.50 | + 1.50 | 12 | 187.00 | 182.00 | − 5.00 |
| 29 | | | | | 15 | 305.50 | 283.00 | −22.50 |
| 14 | 12 | 237.25 | 231.50 | − 5.75 | 17 | 252.50 | 237.25 | −15.25 |
| 15 | 13 | 260.00 | 258.00 | − 2.00 | 14 | 260.00 | 260.00 | 0 |
| 16 | 16 | 225.75 | 222.25 | − 3.50 | 13 | 222.25 | 206.75 | −15.50 |
| 17 | 14 | 139.00 | 145.75 | + 6.75 | 12 | 152.50 | 139.00 | −13.50 |
| 18 | 15 | 154.50 | 148.50 | − 6.00 | 11 | 148.50 | 144.00 | − 4.50 |
| 24 | 13 | 164.25 | 163.00 | − 1.25 | | | | |
| 19 | 13 | 193.00 | 197.00 | + 4.00 | 13 | 197.00 | 193.50 | − 3.50 |
| 30 | | | | | 4 | 183.75 | 183.00 | − 0.75 |
| 25 | 7 | 194.00 | 198.50 | + 4.50 | | | | |
| 31 | | | | | 18 | 156.50 | 143.00 | −13.50 |
| 32 | | | | | 8 | 192.50 | 187.25 | − 5.25 |
| 33 | | | | | 6 | 211.75 | 208.50 | − 3.25 |
| 34 | | | | | 12 | 217.50 | 208.00 | − 9.50 |
| 35 | | | | | 6 | 196.50 | 190.25 | − 6.25 |
| Total | 338 | 5,070.00 | 5,061.50 | − 8.50 | 390 | 6,146.75 | 5,938.00 | −208.75 |
| Average | 13 | 195.00 | 194.70 | −0.33 ± 0.80 | 13 | 204.90 | 197.90 | −6.96 ± 0.60 |

## Reports of cases

***Patient 4.*** This 66-year-old housewife had had diabetes for 12 years; the disease had been regulated by diet and 35 U. of protamine zinc insulin daily. Her height was 59½ inches. The results of complete blood count were normal. There had been occasional glycosuria, but the urine was normal at this time. The cholesterol level was 313 mg. per 100 ml., the basal metabolic rate 1 per cent. Chest x-ray showed calcific plaque in the aortic knob.

Administration of tablet 1 was begun, and she lost 3 pounds in 14 weeks. She was then given tablet 2. After 14 weeks, she had lost 8.25 pounds and experienced no undesirable effects.

Table II gives periodic data.

***Patient 16.*** A 69-year-old housewife had an initial diagnosis of borderline hypothyrodism and obesity. She was 62 inches tall. The complete blood count and urinalysis results were normal. The result of the Mazzini test was negative. A 210 mg. per 100 ml. cholesterol level, a normal electrocardiogram, a 16 per cent basal metabolic rate, 16 per cent $I^{131}$ uptake, and a 21 per cent conversion ratio were recorded.

Tablet 1 was started. During a 19 week course,

**Table II.** *Patient 4*

| *Date* | *Weight (pounds)* | *Blood pressure* | *Pulse* | *Comment* |
|---|---|---|---|---|
| Oct. 4 | 140.50 | 155/80 | 84 | Received tablet 1 |
| Nov. 4 | 137.75 | 132/84 | 60 | |
| Nov. 18 | 138.75 | 120/82 | 80 | |
| Dec. 2 | 140.00 | 154/80 | 72 | |
| Jan. 6 | 141.25 | 138/70 | 68 | |
| Jan. 20 | 137.25 | 142/84 | 76 | Changed to tablet 2 |
| Feb. 3 | 134.75 | 130/66 | 72 | |
| March 2 | 133.00 | 150/70 | 88 | |
| March 16 | 132.00 | 140/68 | 78 | |
| March 30 | 130.50 | 150/70 | 80 | |
| April 27 | 129.25 | 140/70 | 80 | Study completed |

she lost 3.5 pounds. She complained of leg edema on one occasion and received meralluride intramuscularly. When administration was switched to tablet 2, she said almost at once that she noticed a difference, felt well, and lost her craving for food. In the subsequent 13 weeks, she lost 15.5 pounds.

The data are reported in Table III.

***Patient 17.*** A 69-year-old janitress who had been a known diabetic for 5 years had been managed on diet alone. Three years before, she had weighed 220 pounds; she was referred for further weight reduction at the level of 152.25 pounds. Her height was 61¾ inches. Results of complete blood count and urinalysis were negative. The blood sugar level was 114 mg. per 100 ml., the cholesterol level 95 mg. per 100 ml., and the blood urea nitrogen level 15 mg. per 100 ml. A normal electrocardiogram was recorded. The basal metabolic rate was 11 per cent, the $I^{131}$ uptake 35 per cent, and the conversion ratio 40 per cent.

The patient was given tablet 2 and in 12 weeks had lost 13.5 pounds. She was then supplied with tablet 1. Gastric distress developed. Not only did the downward trend in weight stop, but she gained during this phase.

See Table IV.

***Patient 36.*** This 17-year-old obese schoolboy had always been overweight, particularly so from age 10 onward. He admitted to a large food intake and to eating between meals. The boy's height was 71½ inches. Complete blood count and urinalysis had normal results. The blood sugar level was 91 mg. per 100 ml. and the cholesterol level 120 mg. per 100 ml. The basal metabolic rate was −3 per cent, the $I^{131}$ uptake 34 per cent, and the conversion ratio 55 per cent.

The patient was given tablet 2. He lost 10.25

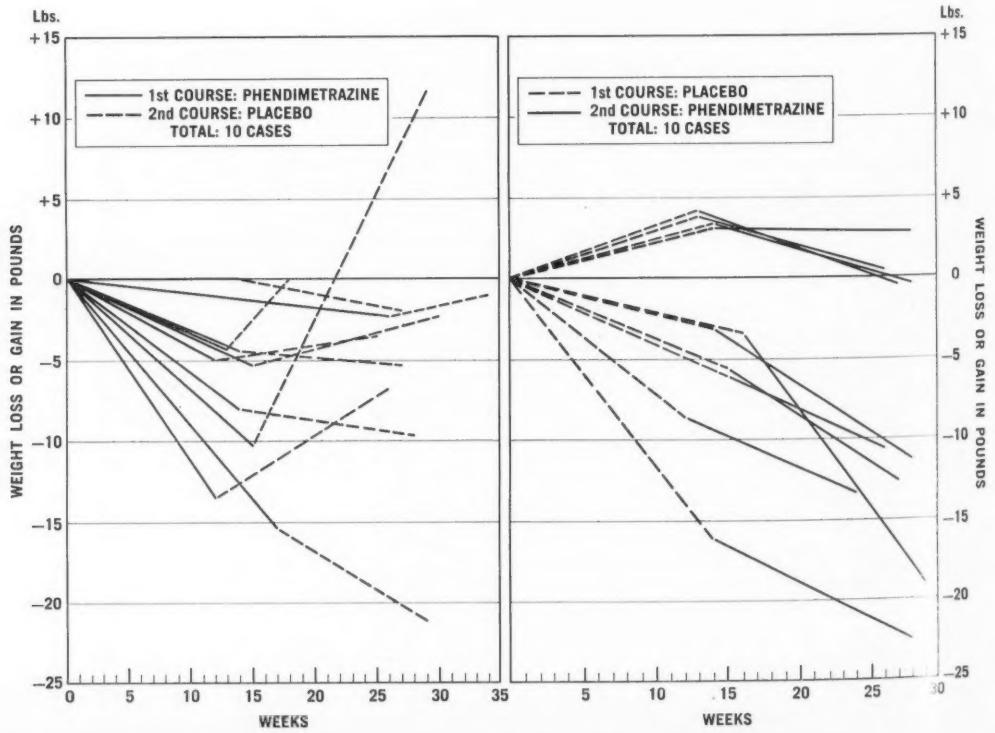


**Fig. 3.** Results with both phendimetrazine and placebo (20 patients).

**Table III.** *Patient 16*

| *Date* | *Weight (pounds)* | *Blood pressure* | *Pulse* | *Comment* |
|---|---|---|---|---|
| Sept. 7 | 225.75 | 110/80 | 84 | Received tablet 1 |
| Sept. 21 | 223.75 | 124/80 | 72 | |
| Nov. 18 | 223.50 | 120/80 | 60 | |
| Dec. 2 | 221.00 | 140/70 | | |
| Dec. 16 | 221.25 | 130/80 | 76 | |
| Jan. 27 | 222.25 | 152/88 | 80 | Changed to tablet 2 |
| Feb. 10 | 217.00 | 130/76 | 96 | |
| Feb. 24 | 213.00 | 130/82 | 72 | |
| March 23 | 210.75 | 132/82 | 76 | |
| April 27 | 206.75 | 130/60 | 76 | Study completed |

**Table IV.** *Patient 17*

| *Date* | *Weight (pounds)* | *Blood pressure* | *Pulse* | *Comment* |
|---|---|---|---|---|
| Dec. 16 | 152.25 | 174/92 | 80 | Received tablet 2 |
| Dec. 30 | 145.50 | 150/92 | 88 | |
| Feb. 24 | 137.00 | 150/82 | 72 | |
| March 9 | 139.00 | 150/75 | 84 | Changed to tablet 1 |
| April 6 | 143.50 | 170/80 | 60 | |
| April 20 | 142.50 | 180/84 | 84 | Tablets made her nauseous |
| May 4 | 145.00 | 170/80 | 80 | |
| June 1 | 146.00 | 172/84 | 60 | |
| June 15 | 145.75 | 142/76 | 72 | Study completed |

pounds in 15 weeks. On changing to tablet 1, he gained 22 pounds in 14 weeks. After the first 2 weeks on tablet 2, he complained of a "gagged feeling in throat." He said he was jittery occasionally on tablet 1, he developed pimples, and he thought the medication was weak.

Table V records the data.

### Comment

The objective in the treatment of obesity is not only to reduce weight but to establish sound eating habits essential to permanent weight reduction. Any unusual, abnormal, or faddish diet will fail after the novelty wears off. It has been our own experience that most patients understand the need for restriction of the caloric intake and are easily instructed in the elements of a well-balanced 1,100 calorie diet, but because of underlying anxieties, tensions, and emotional difficulties, they cannot remain on such a program over a period of time without substantial help.[1, 2, 4]

The anorectic agent offers the most practical means of dealing with this problem.[3] The 4 cases cited in detail are typical of the group as a whole and objectively demonstrate the effect of the drug under investigation as compared with the placebo. Case 17 is of special interest because the subject had lost about 70 pounds before she was referred to our clinic. She went on to lose another 13.5 pounds in 12 weeks on phendimetrazine. While with placebo she gained 7 pounds in 14 weeks.

There was a total of 20 such patients receiving both phendimetrazine and placebo. These groups, however, were too small to demonstrate any statistically valid difference between the phendimetrazine/placebo and the placebo/phendimetrazine sequence. Nevertheless, Fig. 3 may graphically illustrate the psychologic impact of the first few weeks of any reducing program, because 6 out of 10 patients lost weight immediately with the placebo.

**Table V.** *Patient 36*

| *Date* | *Weight (pounds)* | *Blood pressure* | *Pulse* | *Comment* |
|---|---|---|---|---|
| Oct. 7 | 250.75 | 110/72 | 84 | Tablet 2 started |
| Nov. 4 | 246.75 | 110/72 | 84 | Choking and gagging feeling |
| Nov. 25 | 242.00 | 130/84 | 80 | |
| Dec. 30 | 240.75 | 108/64 | 88 | |
| Jan. 13 | 245.25 | 124/74 | 80 | |
| Feb. 10 | 240.50 | 112/72 | 80 | Changed to tablet 1 |
| Feb. 27 | 250.00 | 150/90 | 84 | |
| March 23 | 255.50 | 116/74 | 76 | "Pills weak" |
| April 6 | 257.00 | 115/60 | 80 | Felt jittery |
| May 4 | 262.50 | 115/80 | 84 | Study completed |

**Summary and conclusions**

Fifty obese patients participated in the clinical investigation of phendimetrazine bitartrate using a double blind crossover design. Twenty patients completed both phases of the study, and 36 completed at least one adequate course. A comparison of the two groups showed no significant difference in drop-outs or undesirable effects. The over-all incidence of subjective complaints and minor toxic reactions was negligible; examination, including pulse, blood pressure, blood count, and urinalysis, showed no evidence of major change.

Patients who received phendimetrazine demonstrated an average weight loss of 6.96 pounds, at a rate of 0.54 pound per week. This was about 20 times as much as that of patients who received the placebo; the latter lost an average of 0.33 pound, at a rate of 0.025 pound per week.

The phendimetrazine bitartrate used in this study was supplied as Plegine by Ayerst Laboratories, New York, N. Y.

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# Clinical pharmacology of anticonvulsant compounds

*This review has integrated recent anticonvulsant pharmacologic data derived from both the clinical and experimental approaches in a way meaningful to the practicing physician, clinical investigator, or neuropharmacologist. It is hoped that if these groups use the same language, the epileptic patient may profit.*

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In 1857, Locock[73] demonstrated the efficacy of bromides in the control of catamenial seizures. During the ensuing 100 years, clinical medicine has known a succession of compounds which have served in a variety of ways in the fight against epilepsy. None have been ideal or universally applicable. These various agents have been evaluated largely by empirical methods, so that there are very few published reports of carefully designed clinical trials. Nevertheless, such products as phenobarbital, diphenylhydantoin, and trimethadione were so impressive in the clinic that it was clear to everyone a major breakthrough had been achieved. Because of the paucity of clinical pharmacologic data, the evaluation of the multitude of anticonvulsant drugs introduced in recent years requires that much weight be attached to information derived from animal experimentation.

## Epileptogenesis

Epilepsy, like hypertension, is an event which may be provoked by a variety of stimuli. It is recognized electrically as abnormal synchronous firing of central nervous system mechanisms. The clinical manifestations depend upon mechanisms which are thrown into activity either directly by the focal discharge itself or by virtue of the propagation of hypersynchronous firing to other parts of the central nervous system. One property of such hypersynchrony is a momentary denial of integration and selective coding in highly developed systems. Thus, responses inappropriate to external, internal, and cognitive demands occur. The seizure discharge may be a manifestation of excitation, inhibition, or both.

The brain of the epileptic person has an area or areas the neurons of which are biochemically and metabolically altered, perhaps as a result of chronic ischemia as postulated by Penfield and Jasper[97] or by other unknown but irritative processes which result in abnormal stimulation and discharge rates.[112]

Many of the features of epilepsy remain unknown, but enough information is developing to point the researcher toward new avenues of understanding and the clinician toward more rational therapy.

Received for publication June 5, 1961.

### General pharmacology of anticonvulsants

Toman and Goodman[121] have proposed three ways in which anticonvulsant agents may act: (1) on nonneural tissue such as blood vessels, thus affecting an epileptogenic focus indirectly, (2) directly on neurons involved in the epileptogenic focus to prevent their discharge, and (3) by suppression of activity in neighboring normal neurons to block the spread of seizure discharge. With respect to the first of these, Kennedy, Anderson, and Sokoloff[62] found the interictal cerebral blood flow to be significantly lowered in epileptic children. This was not observed in a similar study in adult epileptics.[44] Aird[1] suggests the anticonvulsant action of diphenylhydantoin involves the stabilization of capillary permeability in the brain. This action would regulate the salt and water shifts in and out of the blood brain barrier, glial tissue, and neurons. Other agents which may function by regulation of acid-base balance, electrolyte shifts, and the state of hydration would also influence neural and nonneural mechanisms. The action may be so indirect as to influence the activity of endocrine systems such as adrenal cortex. Diphenylhydantoin,* for example, is known to possess some ability to affect adrenal cortical secretion.[19, 139]

Several laboratories have presented excellent electron microscopic evidence that the brain is solidly packed with cellular elements without any significant extracellular space.[38, 79] They have suggested that the glial cells constitute the blood brain barrier acting, as it were, between the capillary and the neuron. It is possible, but not proved, that metabolic abnormalities of the glial barrier may lead to neuronal hypersynchrony. Thus the possibility exists that anticonvulsant drugs may act by restoring normal glial barrier mechanisms and thereby indirectly influence nerve cells.

It is interesting to note Ramón y Cajal suggested many years ago that glial cells performed a more active function than merely providing a supportive framework. Only within the past few years, however, have the possible functions of glial cells received the attention of investigators.[57, 138]

The possibility that anticonvulsant drugs may act upon the chemically altered neurons of the epileptogenic focus to prevent their excessive discharge is suggested by the fact that certain early childhood seizures[20, 56] and those caused by isoniazid[125] are both responsive to pyridoxine. Tower[126] has shown abnormalities of glutamic acid, γ-aminobutyric acid, and acetylcholine and of electrolyte metabolism in the human epileptogenic focus. Attempts to use glutamic acid and γ-aminobutyric acid in the management of clinical seizures have been disappointing, however, perhaps because of the difficulty these substances find in crossing the blood brain barrier.

The mechanism of action of most currently available anticonvulsants seems to involve an action on normal neurons so that spread of the seizures discharge from the epileptogenic focus is blocked.

The propagation of seizure discharge from a focus or foci may involve corticocortical, corticosubcortical, or subcorticocortical pathways, depending on the clinical type of seizure. It is apparent that various anticonvulsants have some specificity in raising the thresholds to rapid discharge and hypersynchrony in different pathways.

The cortical dendritic responsiveness may be abnormal in epilepsy.[133] The direct cortical response (DCR) as an index of dendritic activity, and the influence of drugs thereon, has been investigated in experimental epilepsy.[137] This technique should prove valuable in screening anticonvulsant agents.

### Clinical pharmacology of specific compounds

The ideal anticonvulsant would be one that could prevent any epileptic discharge without regard to its pathologic and neurochemical nature or factors of provocation. It should also be indifferent to the location

*Dilantin.

within the central nervous system of mechanisms which possess different thresholds of excitability, autorhythmicity, and means of propagation. The ideal compound should be free of untoward effects, toxicity, and sedation. No compounds which fulfill these criteria are known to pharmacology. There are very few epileptic patients, however, who cannot benefit when an interested and informed physician provides a drug or drugs selected on the basis of his knowledge of the patient and his illness and of the drugs to be used.

***Barbiturates.*** In 1912, phenobarbital was introduced to clinical medicine. In the same year, Hauptmann[52] found it to be superior to bromides for treating seizures. Phenobarbital is an anticonvulsant of proved usefulness when used either alone or in combination with other compounds. In general, its limitation lies in an unwanted sedation. Toxicity and untoward effects are fortunately rare in anticonvulsant dosage.

Phenobarbital, which is slowly but completely absorbed from the intestines, is eliminated by both the liver and kidney.[78] It is not converted to any other metabolite which possesses anticonvulsant activity. Mephobarbital,* however, which is reported to be less sedating and, by some, more useful in the treatment of epilepsy, is incompletely absorbed from the gastrointestinal tract and depends upon degradation to phenobarbital for anticonvulsant action.[14]

The short-acting barbiturates such as pentobarbital appear to enter the brain more rapidly than phenobarbital.[127] The equilibrium time after an intravenous dose of phenobarbital is approximately 12 minutes from its entrance into the brain. Brain concentration in percentage of plasma is then approximately 60 and seems to be uniform in all species.[127] The excretion of phenobarbital is via the urinary tract at the rate of 14 to 18 per cent every 24 hours, and it is excreted unchanged in 25 per cent of the total dose or as a *p*-hydroxyphenyl derivative of which 50 per cent may be conjugated.[15]

The mode of action of phenobarbital as an anticonvulsant is not completely understood, but a number of valuable observations have partly clarified the mechanisms.

Barbiturates appear to exert a greater depressant action on multineuronal transmission systems which possess the greatest number of synapses.[24] Thus, it effectively blocks conduction through the multineuronal reticular formation to depress consciousness.[3] Any such suppression of cortical arousal via the ascending reticular system, however, might possibly increase thalamic synchrony[64] and facilitate those seizures characterized by slow synchronism, such as petit mal or sleep-activated seizures of whatever type.

Another aspect of barbiturate action may be the stabilization of the membrane of the neuron[12]; Goldring and O'Leary[39] found that pentobarbital, in addition to producing electroencephalographic "spindles," produces a positive shift in the DC potential. Seizure-inducing strychnine, on the other hand, produces a negative shift in the DC cortical potential before the seizure occurs. This barbiturate shift in the DC potential may find a chemical and metabolic basis in salt and water transfer which would hyperpolarize the neuron or its dendritic tree. Hyperpolarization thus produced by barbiturate would raise the threshold to repetitive firing.

Morrell, Bradley, and Ptashne[88] produced a chronic epileptogenic lesion in rabbits by the freezing technique. Phenobarbital produced only a slight suppression of the primary focus and transcortical spread but limited subcortical spread of the seizure discharge to the basal diencephalon and protected against pentylenetetrazol* challenge. More recently, the same authors have found that phenobarbital, but not diphenylhydantoin or chlorpromazine,† will

*Mebaral.

*Metrazol.

†Thorazine.

prevent the development of a secondary epileptogenic focus when a primary focus has been established.[89] Vastola and Rosen[131] found seizure spread from focal electrical stimulation in the cat neocortex to be markedly depressed by phenobarbital in a dose comparable to that found effective in terminating status epilepticus in man. Pentobarbital* produced similar results. Analyzing the afterdischarge following cortical stimulation in the cat, Strobos and Spudis[118] found that phenobarbital produced no change in the afterdischarge or the seizure threshold but produced a striking reduction in the duration and spread of the afterdischarge to all regions. Subcortically evoked afterdischarge rarely spread to the reticular formation, cortex, or other subcortical structures of the contralateral hemisphere and spread was much less to adjacent subcortical areas after phenobarbital. Rovit, Hardy, and Gloor[106] found intracarotid amobarbital suppressed an epileptogenic focus in the experimental animal if the focus was in the cortical area of the arterial perfusion. If the focus was a subcortical one or in the opposite hemisphere, amobarbital in either carotid would often cause an instantaneous activation of seizure and spread widely to both cortical areas. This parallels the results seen by the same group in human activation studies.[107, 108]

***Diphenylhydantoin.*** The introduction of diphenylhydantoin by Merritt and Putnam[83] in 1938 constituted a major advance in the therapy of epilepsy. After a single oral dose of diphenylhydantoin in animals and man, absorption takes place slowly from the gastrointestinal tract, reaching the maximum in approximately 12 hours.[23] Noach, Woodbury, and Goodman,[93] using $C^{14}$-labeled diphenylhydantoin, pointed out that virtually all the administered amount can be found in the patient's urine by 48 hours. At 24 hours, however, only 50 per cent has been excreted in the urine, the remainder being in the gastrointestinal tract. Diphenylhydantoin is apparently concentrated in the bile, excreted into the gastrointestinal tract, reabsorbed from the intestine into the systemic circulation as *p*-hydroxyphenyl derivatives, and then excreted via the kidneys. It is also excreted by the salivary glands. Svensmark, Schiller, and Buchthal[119] studied the blood levels with chronic oral and intravenous diphenylhydantoin in man. The rise time of the serum concentration with orally administered diphenylhydantoin was proportional to the dose, reaching a high in 10 to 14 days. A cumulative effect was seen in patients who took diphenylhydantoin for 6 months or more. On withdrawal of the medication, there was a 10 per cent fall of the serum concentration within 12 hours. Within 24 hours, there was an exponential fall of 35 to 55 per cent as compared to a 75 per cent decrease in serum concentration in the case of phenobarbital. The same serum concentration was observed after 18 hours whether the drug was given intravenously or orally. The concentration in the cerebrospinal fluid was only one-half that of the serum after prolonged therapy. The brain concentrations of diphenylhydantoin seem to be equivalent to the plasma concentration, and the brain serum equilibrium time recorded after an intravenous dose is 15 minutes according to Fisher and Staub.[28]

Buchthal, Svensmark, and Schiller,[13] in an excellent study, correlated the concentration of diphenylhydantoin in the serum with the clinical course, electroencephalographic changes, and drug toxicities in patients with grand mal epilepsy. They found that the clinical improvement in patients with grand mal epilepsy required a concentration of diphenylhydantoin in the serum of 10 to 20 $\mu$g per milliliter. This corresponds to a dosage of 4 to 7 mg. per kilogram of body weight; 6 to 10 days of oral administration were required to reach such blood levels. In all but 1 of 12 patients with severe grand mal epilepsy on whom daily electroencephalograms were recorded, the amount of paroxysmal activity decreased by more than half when the

*Nembutal.

serum level of diphenylhydantoin reached 10 μg per milliliter. On the other hand, only half of the outpatients whose serum concentration was above 10 μg per milliliter showed a reduction in the incidence of paroxysmal activity, and half of the outpatients whose serum levels were below 10 μg per milliliter showed an increase in paroxysmal activity as compared with previous tracings. Thirty-eight patients who received known amounts of diphenylhydantoin per day for 2 to 3 weeks showed evidence that 5 to 8 mg. per kilogram was necessary to obtain a serum level of 10 to 20 μg per milliliter. Such a concentration in a person of 70 kg. would require a daily dose of 350 to 550 mg. of diphenylhydantoin. On the other hand, 29 patients who had taken diphenylhydantoin in the hospital for more than 6 months needed only 3 to 5 mg. per kilogram to maintain the same serum levels. This is evidence of a cumulative effect, at least when medication is constantly taken. This demonstrates that the physician's chore is not completed by a prescription pad, since outpatients do not invariably take medicine as prescribed.

The incidence of toxic effects was also correlated with serum concentrations in 174 patients. Pronounced toxic effects did not occur with serum levels below 30 μg per milliliter and were seen in half of 34 patients with serum diphenylhydantoin levels of 30 to 60 mg. per milliliter. None of the patients with serum concentrations below 14 μg per milliliter had toxic effects. Increased tolerance to the toxic effects of diphenylhydantoin was indicated by the finding of a greater incidence of such effects among patients who had taken the drug for less than 6 months than among those who had taken it for a long period.[13]

Morrell, Bradley, and Ptashne[90] found that parenteral diphenylhydantoin caused peripheral nerves to exhibit a rise in threshold to stimulation. There were a decrease in spike amplitude to supermaximal stimulation and a prolonged synaptic delay or conduction time. With long duration currents, the rebound spike commonly seen was abolished. These experimental findings led to the beneficial use of diphenylhydantoin in the therapy of trigeminal and glossopharyngeal neuralgia.[58] Green[45] reported similar results in controlling tabetic pain.

A mode of action assumed for diphenylhydantoin is the inhibition of progressive spread of seizure discharge in the brain.[122] A further assumption has been made that this effect is due to the inhibition of posttetanic potentiation. Diphenylhydantoin markedly decreases the brain neuronal sodium concentration by some mechanisms which seem to increase the turnover rate within the cell so that the rate of efflux predominates over influx. This central nervous system cellular decrease in permeability to sodium would decrease posttetanic potentiation. The net effect is a reduction in both irritability and frequency response of the neuron. This mechanism of electrolyte stabilization may be related to the chemical changes in amino acid metabolism which are induced by diphenylhydantoin in brain cells.[140]

Vastola and Rosen[131] found the neocortical spread of a seizure induced by cortical stimulation in cats was markedly depressed by diphenylhydantoin as well as phenobarbital. Afterdischarge propagation to stimulation of the cortex, hippocampus, and amygdala as well as the septum was depressed by diphenylhydantoin. The propagation of amygdala seizures to hippocampus and cortex was not influenced by diphenylhydantoin.[118] This may explain its lack of effect in most psychomotor seizures. When chronic epileptogenic lesions were made by the freezing technique in experimental animals, diphenylhydantoin in high doses was unable to suppress the primary focus; it did, however, suppress transcortical spread of the seizure activity but did not prevent the spread to the basal nuclei which is responsible for bilateral synchronous paroxysm. It also offered no protection against pentylenetetrazol challenge.[88] This information may offer some insight into how a certain medication may be either ineffective by its lack of influence on a pri-

mary focus or only partially effective by the lack of suppression of several projection mechanisms. For instance, if diphenylhydantoin suppresses transcortical spread but does not influence spread to subcortical systems, the seizure may be seen as a partial one such as a "centrencephalic," petit mal, or even a psychomotor type. Toman[123] reports similar clinical observations.

It seems possible to obtain similar data with implanted electrodes in epileptic patients preceding neurosurgical removal of epileptogenic foci. The response to anticonvulsant medication in this setting would offer valuable information concerning drug influence on the electrophysiologic abnormality of seizures. Such information is not available at present.

An extrapolation of the above information to a mechanism outside the central nervous system is not difficult. Diphenylhydantoin has been used successfully to block induced cardiac arrhythmias[51, 91, 111] and clinically occurring ventricular tachycardia unresponsive to procaine amide.*[69]

The reader is referred to other sources for general remarks about diphenylhydantoin toxicity.[40] Ataxia and nystagmus seem to be related to the cerebellar effects of diphenylhydantoin. The cerebellar signs are usually temporary, but very high intravenous doses of diphenylhydantoin have been shown to produce lesions in the cerebellum.[54]

Diffuse pulmonary fibrosis has been reported to be a result of chronic dilantin therapy.[87] Others fail to confirm this finding.[70] Gingival hypertrophy is common and may be related to the excretion of dilantin in saliva. Antihistaminic agents have been used but seem less important in its prevention than continuous dental hygiene.

The hematologic abnormalities caused by diphenylhydantoin include megaloblastic anemia,[29, 110] which is responsive to folic acid but not vitamin $B_{12}$.[7]

German workers have reported finding L.E. cells in 7 patients on long-term hydantoin therapy. Three had clinical lupus erythematosus. The other 4 showed minimal or no symptoms.[109] This untoward reaction must be investigated further.

The efficacy of diphenylhydantoin, especially in the treatment of major motor seizures, is well established. This is especially true if it is combined with phenobarbital. It is less effective than other agents in the treatment of psychomotor seizures and of little or no value in petit mal. With the availability of parenteral diphenylhydantoin, persons with status epilepticus can be treated without the marked sedation which results from the necessary dosage of barbiturates.[113] Intravenous administration is also helpful in preventing seizures when the oral route is contraindicated.

Methylphenylethyl hydantoin,* another hydantoinate, has shown no clinical advantage over diphenylhydantoin. The greater incidence and severity of toxic reactions caused by mesantoin deny its present-day acceptance as an anticonvulsant drug.

***Trimethadione.*** Trimethadione† was introduced by Richards and Perlstein.[102] It is rapidly absorbed from the gastrointestinal tract and rapidly reaches an equilibrium concentration of 50 per cent of the plasma level within the brain. It is slowly excreted in the urine at about 2 to 4 per cent per day and is excreted as a dimethyloxyzolidone derivative.[127] To date, there has been very little neurophysiologic or neurochemical research which would point to the mechanisms of action of trimethadione in petit mal epilepsy. Testing the effects of trimethadione on electrical stimulation seizures in rabbit cortex and diencephalon, Gangloff and Monnier[35] found that it increased the threshold for after discharge in cortex and diencephalon and reduced the duration of the afterdischarge of the cortex. Other workers found that seizure which spread over the cat neocortex, although markedly depressed by both di-

*Pronestyl.

*Mesantoin.

†Tridione.

phenylhydantoin and phenobarbital, was not altered by trimethadione.[131] In an experimental design perhaps more analogous to a clinically appearing event, Morrell, Bradley, and Ptashne[88] found that trimethadione modified a cortical epileptogenic focus by first producing a clear-cut activation of the focal discharge with an extensive spread along the ipsilateral cortical surface. This was a rather slow spread and was not felt to be a dissemination of paroxysmal activity by way of diencephalic nuclei. Early activation was later replaced by a marked suppression of the focal cortical discharge and a normalization of the record which was more pronounced than with any other drug tested. Pentylenetetrazol was capable of reactivating the cortical focus, but neither generalized paroxysmal discharge nor clinical seizure could be produced. In fact, trimethadione completely protected the animal against a test dose of pentylenetetrazol. Trimethadione thus seemed to be capable of suppressing the primary epileptogenic focus as well as limiting its spread to the basal diencephalon. Cortical spread, however, was not effectively limited by trimethadione until the primary focus itself was suppressed. The authors regard the early activation by trimethadione to be perhaps related to inactivation of inhibitory mechanisms within the diencephalon. The experimental evidence for this, however, is lacking.

In man, trimethadione is the most effective agent in petit mal. Within the first 24 hours of trimethadione therapy, a patient may experience a sharp increase in seizures[41]; when therapy is continued at this same dosage level, a complete clinical remission may well occur. This is in keeping with experimental observations of Morrell, Bradley, and Ptashne.[88] Trimethadione therapy can revert the 3 per second spike and wave electroencephalographic pattern to a more normal rhythm. Provocation of the spike and slow wave discharge by hyperventilation is less likely.[123] Although trimethadione possesses little effectiveness against major motor or psychomotor seizures, it may be a valuable adjunct if a grand mal seizure pattern shows electroencephalographic evidence of slow wave dysrhythmia.[41] Even in psychomotor seizures, trimethadione may be helpful as an adjunct if hyperventilation activates spike and slow waves in the electroencephalogram.[124] However, it is apparently without effect in "petit mal variant" dysrhythmias and hypsarrythmia. Trimethadione may be useful in a clinical application to control symptomatic seizures which also have slow wave dysrhythmias from cortical and subcortical lesions caused by inoperable neoplasia. The experimental evidence in man[41] and in animals[88] would seem to lend substance to such a concept. Focal cortical seizures may also respond to trimethadione in some situations.

Despite its effectiveness in comparison with all other agents in the control of petit mal epilepsy, trimethadione can be seriously toxic.[40, 136] The toxicity includes hematologic disturbances which in some instances have been fatal.[31] Hepatitis, dermatitis, and hemeralopia and scotomas may also occur and require discontinuance of the drug. A nephrotic syndrome and other nephrotoxic effects of trimethadione have been reported.[84, 104] More recently, alopecia has been reported as a reversible side effect of trimethadione therapy.[55]

The substitution of a less toxic but related single agent such as paramethadione* generally offers the patient much less effective therapy.[142] Trimethadione should be employed only if less toxic drugs are ineffective.

***Primidone.*** Primidone† was introduced in 1952 by Handley and Stewart.[49] It has been used in a number of reported series[47, 71, 80, 114] but has not been subjected to adequately controlled clinical trials. It would appear from the available data that it is about as effective as phenobarbital in controlling grand mal seizures and may have a salutary effect on patients with psycho-

*Paradione.
†Mysoline.

somotor seizures. Toxic effects include troublesome drowsiness, dizziness, ataxia, nausea and vomiting, rash, personality changes, and dyplopia. Less frequent untoward effects were impotence, slurred speech, paranoid psychosis, polyuria, abdominal pain, leukopenia, and anemia.[71] Megaloblastic anemias have been reported from primidone.[34] It has also been reported to increase the frequency in number of petit mal seizures.[46]

Chemically, primidone resembles phenobarbital quite closely. In a series of laboratory screening tests designed to check the spectrum of anticonvulsant activity, it was found to be a less potent anticonvulsant agent than phenobarbital.[42] At least 20 per cent of the primidone circulating in the body is converted to phenobarbital.[16] This accounts for at least some of its anticonvulsant action but does not seem sufficient to explain either the incidence or type of untoward effects reported or its apparent effectiveness against psychomotor seizures. In order to reduce the incidence of toxic effects, primidone therapy should be started slowly in a single nocturnal dose, and within 1 to 2 weeks, it may be increased as needed.[120]

***Succinimide derivatives.*** In the case of all three of these compounds, phensuximide,* methsuximide,† and ethosuximide,‡ there is a dearth of experimental and clinical pharmacologic information.

Phensuximide possesses some effectiveness in the therapy of petit mal either alone or in combination with other drugs. Complete control in 20 per cent of 200 patients with petit mal epilepsy was achieved, and seizures were reduced by 80 per cent in the entire group when compared to the previous medications used.[143] The untoward effects reported were hematuria, dizziness, drowsiness, abdominal pain, itch and rash, nausea, vomiting, and decrease in appetite.[143] Minor nephrotoxic symptoms have also been reported in British studies.[84] In the hands of others, in which phensuximide caused few toxic reactions, there also was a negligible ability to control petit mal seizures.[101, 142]

Methsuximide, a newer relative of phensuximide, has enjoyed wider use. Zimmerman and Burgemeister,[144, 145] comparing methsuximide with either the previously used medication or placebos, felt that it is an effective medication and compares favorably with trimethadione in the control of petit mal seizures. It is also a useful adjunct in the treatment of psychomotor seizures.[146] In another study, methsuximide was given to patients with a variety of seizure disorders that had been refractory to other medications. Complete control of seizures was seen in 10 per cent of patients with grand mal, petit mal, and focal seizures. Fifty per cent obtained no effect whatsoever, and 10 per cent were made worse while on methsuximide. No patients with psychomotor seizures obtained complete relief, and only 1 obtained practical control. The untoward effects noted included some signs of liver toxicity, edema, albuminuria, skin rashes, drowsiness, and unsteadiness. Personality changes were noted especially in patients with psychomotor epilepsy. Two such patients were hospitalized because of psychosis occurring during treatment.[26]

Ethosuximide is the newest of the succinimide derivatives. Early reports by Zimmerman and Burgemeister[147] and Gordon[43] suggest that ethosuximide, in contrast to methsuximide, does not possess a broad spectrum of anticonvulsant activity but is primarily effective against petit mal epilepsy, including that refractory to previous therapy. In addition, ethosuximide provided complete control in 29 to 40 per cent of patients with mixed epileptic attacks, including psychomotor episodes.[147] When ethosuximide is given to patients with mixed petit mal and grand mal seizures, it tends to increase the grand mal attacks if medication for the major motor seizures is insufficient. So far, the only unto-

*Milontin.
†Celontin.
‡Zarontin.

word effects reported are drowsiness, dizziness, nausea, and gastric distress. Differing from other anticonvulsants, tolerance to ethosuximide has not occurred.[147] Vossen[134] reported several hematologic changes that occurred in patients on ethosuximide therapy; however, it is not obvious that these could be attributed to ethosuximide, since most patients were on combination therapy. The same author mentions a curious lack of correlation between clinical improvement and improvement of the electroencephalographic pattern.

Lorentz de Haas[77] finds ethosuximide to be effective in treating generalized and minor seizures, some of which may be classified as psychomotor. The same report mentions a 5 per cent incidence of psychoses during seizure-free periods when the electroencephalograph showed "forced normalization" as described by Landolt.[68]

To date, available evidence suggests the succinimides, especially methsuximide and ethosuximide, are effective agents against minor seizures with a minimum of untoward reactions. But enthusiasm should be restrained until more controlled observations and basic studies are reported.

***Phenacetylurea.*** Phenacetylurea (phenacemide)* is regarded as the most effective anticonvulsant in the treatment of psychomotor (temporal lobe) seizures. The high incidence of personality disturbances and serious toxic reactions involving the hematopoietic, hepatic, and renal systems, however, severely limits its usefulness.[40, 129] For this reason, it will not be considered further.

***Acetazolamide.*** As a carbonic anhydrase inhibitor, acetazolamide† is absorbed rapidly from the gastrointestinal tract and is excreted probably unchanged by the kidney within 8 to 12 hours.[127] Although its concentration in the brain is very small, acetazolamide changes brain excitability by causing carbonic acid retention within cells, a decrease in intercellular sodium, and increasing brain glutamic acid and γ-aminobutyric acid concentration.[140] Epileptogenic foci, both experimentally produced[6] and in human brains,[126] are known to be deficient in these amino acids. Moreover, the decreased cellular permeability to sodium should raise the excitability threshold and decrease the propagated impulse.[140]

Since 1952, various clinics have found acetazolamide to be an effective agent, either alone or with other drugs, in petit mal management.[5, 82] Lomboroso and Forxythe[76] recently found acetazolamide of benefit to patients with either petit mal, myoclonic, akinetic, grand mal, or mixed seizures. It was of no value in controlling psychomotor or focal seizures. Petit mal seizures are reported to be more effectively suppressed by acetazolamide when the patient either shows electroencephalographic activation response or develops clinical seizures with hyperventilation.[21] Millichap,[85] in a double blind controlled study on children with variable seizures, found acetazolamide quite effective in major motor and myoclonic seizures with few side effects. The limiting factor in acetazolamide therapy is the development of tolerance, which markedly decreases its long-term usefulness.

The potentiation of acetazolamide by ammonium chloride has been reported, although by itself ammonium chloride is ineffective.[86] Previously, ammonium chloride, an "acidifier," was found to offer assistance to all types of seizure patients, especially when the agent added to previous medication.[61] The deficient glutamine content of the seizure focus and hyperexcitability of the brain apparently can be corrected with the increase of ammonia substrate.[99] Correcting the amino acid deficit may decrease the excitability of a seizure focus.[128] For these reasons, ammonium chloride deserves a second experimental look as an anticonvulsant.

***Aminoglutethimide.*** Within the past 2 years, several new anticonvulsants have been introduced. Of this group, aminoglu-

*Phenurone.
†Diamox.

tethimide,* a close relative of the soporific agent glutethimide,† has been presented to the medical public as an anticonvulsant in a sketchy and fragmentary manner.[17, 67, 96] At this time, there is not enough evidence to evaluate this compound from either the standpoint of clinical effectiveness or sufficient pharmacologic and toxicologic information.

### Miscellaneous compounds with possible anticonvulsant usefulness

***Tranquilizers.*** There is ample neuropharmacologic evidence that reserpine and chlorpromazine in high doses lower seizure thresholds especially in temporal lobe structures.[63, 100] Clinically, reserpine has been found to increase the incidence of seizures in some patients, especially if central nervous system lesions are pre-existing.[30, 94, 148] Clinical experience with phenothiazines, especially promazine, indicates a convulsive potential[66, 81, 132] especially in patients who have had leucotomy.[11] Nevertheless, reserpine, chlorpromazine, and meprobamate and their near relatives have been used as adjunctive therapy in seizure disorders, with varying results reported. In one study, patients responded to reserpine when combined with previous medication if it decreased the "psychologic triggering mechanisms," but in general, the seizures were increased.[148] In psychotic patients with epilepsy, reserpine seemed to reduce the seizures,[92, 105] chlorpromazine has been reported to have similar results in psychomotor epilepsy,[53] but there has been a report that disturbed epileptic patients show an increase in seizures if the anticonvulsant medication is decreased.[10]

Meprobamate has been reported to be helpful for children with both behavioral abnormalities and minor motor seizures (hypsarrhythmia). Frequency of grand mal seizures, however, was increased.[59, 72, 98]

Unless a patient has a significant psychologic disturbance which makes management difficult or behavior inappropriate after proper seizure suppression, these agents appear to have little place in his therapy.

***Adrenal cortical steroids.*** Desoxycorticosterone has been shown to increase the threshold for electrical excitability and to potentiate anticonvulsants. This effect has been related to changes in the concentration of extracellular sodium.[141] Aird[2] found that intravenous desoxycorticosterone tended to reduce the electroencephalographic abnormalities in patients with petit mal. For 10 refractory epileptic patients, he added desoxycorticosterone to the other medical regimen. Seven patients had a reduction in seizures (petit mal or grand mal). In two instances, the seizures were abolished. When placebos were substituted for desoxycorticosterone, there was a dramatic increase in frequency of seizures. On resumption of desoxycorticosterone therapy, the seizures diminished.

A number of reports in this country and abroad have proclaimed adrenocorticotropic hormone (ACTH) to be proper therapy for the seizure disturbance in early infancy and childhood known as hypsarrhythmia. Stamps and colleagues[115] reported dramatic improvement in 30 per cent of the children under 1 year, with a return to normal of the electroencephalographic pattern, cessation of spasms, and reduction of further mental retardation. They stress the increased effectiveness if ACTH is begun early in the disease process. Hansted[50] reported similar success with ACTH and, in comparing it with phenobarbital and dimedione, thought it to be far more efficient. On the other hand, some have found corticotropin and adrenal steroids to be ineffective in managing hypsarrhythmia and its accompanying mental deterioration.[95]

Seizures are seen in some patients with Cushing's disease. Exogenous adrenal cortical steroids have frequently precipitated seizure states in patients with lupus erythematosus[25] and in patients who have no evidence of central nervous system disease.[37, 116]

*Elipten.
†Doriden.

Possible differences between desoxycorticosterone and corticotropin and the naturally occurring adrenocorticosteroids have been discussed by Woodbury.[139] It is possible that the minor seizures of infancy and early childhood known as hypsarrhythmia may be entirely different from the seizure process seen in adults. Certainly, the use of ACTH and cortisone in most usual types of adult epilepsy is not indicated.

***Amphetamines.*** The amphetamines produce cortical arousal effects similar to those seen with stimulation of the reticular activating system and have been used for some time to prevent sleep. They have also been found helpful as adjunctive therapy in the treatment of petit mal and narcolepsy, but critical studies are not available. Logothetis,[74] observing a group of patients with sleep-activated seizures, found that 65 per cent of his patients experienced a 50 per cent or more decrease in seizures while receiving methamphetamine. Greater effectiveness was seen in those patients whose electroencephalograms showed either synchronous 2 to 6 per second high voltage spike and wave patterns or a 14 and 6 positive spike rhythm. Others have been even more impressed with the effectiveness of methamphetamine in controlling sleep-activated seizures.[48] Experimental evidence which points to a similar relationship between cortical arousal and seizure discharge comes from the work of Gellhorn.[36] Franken and Gunn[32] have recently shown that stimulation of the mesencephalic reticular formation (which causes cortical arousal and alpha blocking) in short bursts may inhibit an acute or chronic epileptogenic focus and prevent the spread of the seizure discharge at the onset of a seizure. However, if arousal is continued over a prolonged period, a seizure may be precipitated.

***Procaine and lidocaine.*** Procaine and lidocaine* are agents which if injected intravenously are also capable of altering high amplitude slow wave electroencephalograms in patients after a cardiac arrest with major motor seizures, causing a low amplitude fast activity which is suggestive of the arousal phenomenon.[48] French and associates[33] have shown that, given intravenously, procaine is capable of protecting against electroconvulsive seizures.

In clinical usage, lidocaine has been found effective in aborting status epilepticus and some Jacksonian focal seizures. It was only of partial effectiveness in patients with seizures following intracranial surgical operation and had no effect on myoclonic seizures.[8, 9]

***Anticholinergic agents.*** Atropine and belladonna in high doses show early promise when used as an anticonvulsant medication in selected patients with minor seizures characterized by a visceral aura.[48]

Both atropine and scopolamine have been shown to be effective in blocking the slow wave abnormalities which follow electroconvulsive therapy. Atropine produced faster low amplitude cortical activity. The slow waves returned within 1 to 2 days after atropine had been discontinued.[27, 130] Ward[135] has shown that atropine in large doses can prevent the slowing of either the electroencephalographic patterns which follow electrically induced seizures or those which occur with closed head injuries.

### Factors influencing clinical pharmacologic response to anticonvulsants

***Psychologic factors.*** Physicians and many epileptic patients are aware that emotionally charged situations may precipitate seizures in spite of anticonvulsant therapy.[18] It is a common observation that persons with previously uncontrolled epilepsy are relatively seizure free in a sheltered environment without any change in medication. These observations have led to the impression among many that whenever seizures are "intractable," strong emotional conflicts may be relevant to their activation. Indeed, some seizures may be precipitated for primary or secondary gain.[103]

*Xylocaine.

These forces must be recognized and modified before anticonvulsant agents can manifest their full pharmacologic effects.

In 1947, Barker and Wolf[4] reported the experimental production of a grand mal seizure during a stress interview. Subsequent studies by Stephens[117] have documented seizure patterns in the electroencephalogram during discussion of emotionally laden topics with epileptics who had normal resting records. Existing electroencephalographic abnormalities were also intensified in some patients by the same technique.

Group psychotherapy has been found useful in the management of epileptic children, especially when the mothers were included in the treatment program. The mothers ultimately displayed more freedom and less anxiety in the children, and seizures in some became less frequent.[22]

Drug treatment of epilepsy is further complicated when the hyperventilation syndrome is present. Careful attention to the history and observation of the effects of deliberate hyperventilation on the patient and his electroencephalogram are helpful, and it is often possible to avoid complicating hyperventilation by thorough instruction of the patient.

Catamenial exacerbation of seizures is well recognized but poorly understood and at times difficult to control. Logothetis[75] presented evidence that estrogens given to women with catamenial seizures provokes paroxysmal electroencephalographic activity and clinical seizures. Progesterone, however, conferred no protection. This work suggests a hormonal activation which may be blocked if estrogenic activity is decreased by more effective techniques. Psychologic changes in the premenopausal woman which are related to the menstrual cycle have also been considered but not critically evaluated as a contributing factor in catamenial epilepsy.

***Underlying disease states.*** Each year, clinics and physicians see a significant number of patients whose seizures are considered "idiopathic" only because the cause has gone unrecognized. Broadly speaking, these conditions include brain tumors, vascular lesions, metabolic or hormonal abnormalities, and the unrecognized consumption of alcohol. Many of these patients fall into the "intractable" category. When diagnostic study is sufficiently thorough, the correction of the underlying cause, if possible, may either effect a cure or render the seizures responsive to medical management. Careful diagnosis is therefore fundamental to the therapy of epilepsy, as with all disorders.

***Omitted medication.*** Often overlooked but very important in complicating the therapy of epilepsy is the patient's failure to take the medication regularly as prescribed. It is well known that sudden withdrawal of any anticonvulsant agent may increase or actually provoke seizures. Patients, especially those who are psychologically upset, may display a troublesome lack of candor in reporting what they have taken. This must be watched for.

***Final comment.*** Drugs are important in the treatment of epilepsy. New drugs continue to appear on the market. The problem of assessment amounts to a serious dilemma.[65] New techniques for evaluation are needed. In this connection, recent efforts to apply sequential analysis to the study of effects of various agents on seizure incidence is of interest.[60] Real progress in the understanding of the pharmacotherapy of epilepsy, however, will await a more critical attitude on the part of editors of journals so that only those therapeutic reports are published which include properly controlled clinical trials and scientific methods of data analysis.

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# Clinical pharmacology of systemic antidotes

*This review is restricted to those agents which are effective by systemic rather than local action. Thus, there are to be found discussions of chelating agents, narcotic antagonists, anticholinesterase antidotes, cyanide antidotes, fluoroacetate antidotes, bemegride, and agents useful in digitalis, methemoglobin, chlorpromazine, amphetamine, anticoagulant, and bromide poisonings.*

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The quest for antidotes has a long history which paralleled early the popularity of poisons as instruments of assassination and more recently the advent of powerful drugs, the prevalence of opportunities for industrial exposure, and the impetus provided by an increased understanding of toxicologic mechanisms.

The early studies of antidotes,[310, 366] indeed even relatively recent studies by Nazi "scientists,"[289] were steeped in nefarious tradition. Ancient tyrants often utilized poisons to dispatch their troublesome contemporaries and, fearing reciprocation, initiated desperate searches for antidotes. As early as the third century B.C., Apollodoros composed a then authoritative treatise on antidotes, in the form of a poem. In the second century B.C., oriental royalty investigated poisonous plants for their homicidal potentialities and, distrusting their colleagues, attempted to develop means of protecting themselves from their own poisons. Probably the first recorded "universal antidote" was introduced in the first century B.C. by Mithridates Eupator and was called *Mithridateios antidotos*. This was later superseded by *thēriacē*, which was invented in Nero's time by the Cretan physician Andromachos. This "antidote" contained no less than seventy-three ingredients and gained much popularity and fame. Unfortunately no universal antidote, including the one popularly advocated for use today, has proved to be either universal or highly effective.

The popularity of poisons, and therefore interest in antidotes, began to wane during the Christian era but revived during the Renaissance when poisoning again became an effective political instrument. Those who utilized it to implement government policy looked upon poisoning as a fine art and upon professional poisoners as artisans. The recognition of industrial poisoning hazards later provided much impetus to the study of poisons and antidotes, and this continues to be a major stimulus.

Most of the early antidotes were either locally acting agents which acted, if at all, to retard adsorption of the poison through chemical reaction or mechanical adsorption or were substances which had nonspecific systemic effects opposite to those exerted

Received for publication April 12, 1961.

by the poison, e.g., a stimulant in poisoning by a depressant. As the understanding of the mechanisms by which various poisons exert their effects has increased, it has been possible to design an increasing number of systemic antidotes, many of which are highly specific and efficient in blocking or otherwise counteracting the effects of poisons. Moreover, investigation of a number of these antidotes has contributed greatly to a clarification of the mechanisms of action of the corresponding drug or poison. For example, much has been learned about the mechanism of action of narcotics through investigation of the narcotic antagonists, and the use of acetate donors as antidotes in fluoroacetate poisoning has added to the knowledge concerning the toxic properties of fluoroacetate. In addition, an understanding of the mechanisms of action of antidotes of proved efficacy provides a good foundation for the development of other antidotes.

The purpose of the present report is to review the human pharmacology and clinical use of those systemic antidotes which are deemed to be the most important from the standpoints of specificity and proved or theoretic efficacy. Whether some of the therapeutic measures which were chosen for discussion should be included in an article which deals otherwise with more or less specific antidotes is admittedly debatable. The decision to include certain measures was made arbitrarily on the bases that their effects seemed to offer distinct improvements over earlier conventional methods of treatment and that they appeared to have an effectiveness which was out of proportion to intrinsic pharmacologic properties, that is to say, the effects which were exerted in the presence of poisoning would be expected to be exerted either not at all or to a significantly lesser degree in its absence (for example, the effective sedation produced by chlorpromazine in amphetamine poisoning occurs with doses of the tranquilizer which per se are devoid of gross behavioral effects, while a comparable quieting effect is obtained with such other sedatives as barbiturates only in distinctly depressant doses). Inclusion of the discussion on bemegride in barbiturate poisoning was motivated by a desire to "set the record straight" since there are many who retain the erroneous impression that this is a specific antidote.

The intention of this paper is not to review exhaustively the voluminous literature relative to the antidotes selected for discussion but rather to discuss that information which is thought to be indispensable to an understanding of their human pharmacology and, therefore, to their rational clinical use. Where adequate previous reviews are available, these are referred to and the literature reviewed therein is not usually reiterated except as this becomes necessary in order to present a complete picture. The emphasis is on studies in human beings, but extensive supplementation with data from animal experiments seemed desirable in many instances because human experimentation was lacking or failed to clarify important points. Commercial sources of supply of many of the antidotes under dis-

**Table I.** *Approximate stability constants of metal-EDTA complexes*

| *Metal* | *Log K** |
|---|---|
| Vanadium (III) | 25.9 |
| Iron (III) | 25.1 |
| Thorium | 23.2 |
| Mercury | 21.8 |
| Copper | 18.8 |
| Nickel | 18.6 |
| Yttrium | 18.1 |
| Lead | 18.0 |
| Zinc | 16.5 |
| Cadmium | 16.5 |
| Cobalt | 16.3 |
| Iron (II) | 14.3 |
| Manganese | 14.0 |
| Vanadium (II) | 12.7 |
| Calcium | 10.8 |
| Strontium | 8.6 |
| Barium | 7.8 |
| Silver | 7.3 |

Compiled from Martell and Calvin,[283] Welcher,[442] and Bjerrum, Schwarzenbach, and Sillén.[34]

*Ionic strength 0.1; 20° C.

**Table II.** *Therapeutic effectiveness of dimercaprol and edathamil in treatment of metal poisoning*

| *Metal* | *Therapeutic efficacy** | | *References† and remarks* |
|---|---|---|---|
| | *BAL* | *EDTA* | |
| Americum | | + | 111, 139 |
| Antimony | + | | A, 3, 47 |
| Arsenic | + | | A, D, 426 |
| Cadmium | (−) | ± | Both complexes nephrotoxic in chronically poisoned animals,[103, 147, 157] but the BAL glucoside may circumvent this problem[157, 414]; EDTA reported effective in acutely poisoned animals[242, 375, 396] and in a few human cases[99] |
| Chromium | (+) | + | Poisoned animals and EDTA treatment of chrome ulcers (B, D).[47] |
| Cobalt | | (+) | 23, 29, 48, 295 |
| Copper | + | + | Enhancement of copper excretion in Wilson's disease (B)[31, 59, 109, 367, 425, 435] and in normal individuals[269, 342]; protection of poisoned animals.[33, 48] |
| Gold | + | | B, D, 89, 280, 336, 407 |
| Iron | (−) | + | BAL may increase toxicity[122]; EDTA enhances iron excretion in iron storage diseases (B),[133, 158] normal persons,[158, 342] and acutely poisoned dogs.[51] |
| Lead | ± | + | A, B, D, 29, 32, 56, 341 |
| Manganese | − | + | A, 319, 322 |
| Mercury | + | ± | A, B, D, 24, 263, 394, 464 |
| Nickel | + | + | A, B, 47, 283 |
| Plutonium | (−) | + | B, C, 139, 303, 304 |
| Radium | (−) | (+) | C, 300 |
| Selenium | (−) | (±) | BAL enhances toxicity[47]; EDTA protected animals against moderate doses but only if given very early.[396] |
| Silver | (−) | | D, 155, 353 |
| Strontium | (−) | − | C, 87, 95, 240, 270, 402 |
| Thallium | −? | −? | Both ineffective in animal studies[47, 267, 275]; clinical reports scanty and conflicting[4, 64, 305, 400, 417] |
| Thorium | | + | A, 192, 469 |
| Tungsten | (+) | (+) | 268, 396 |
| Uranium | − | + | D, 6, 61, 102, 334, 420, 469 |
| Vanadium | | + | EDTA effective in animals (B); enhanced vanadium excretion in normal humans[322] |
| Yttrium | (−) | + | C, 87, 95, 171 |
| Zinc | +? | +? | Excretion enhanced in nonpoisoned human subjects[269, 321, 322, 342] |

*Notations in parentheses indicate information from animal experiments only. Absence of + or − indicates lack of information.

†Letters refer to the following reviews: A, Brieger[49]; B, Chenoweth[74]; C, Schubert[371]; D, Stocken and Thompson.[405]

cussion are listed elsewhere[11]; sources of some of the available newer agents are included in the text.

### Chelating agents in metal poisoning

Chelating agents are organic molecules which are capable of forming complexes with polyvalent metallic ions, thereby rendering the metal unavailable for its usual reactions. The chemistry and pharmacology of chelating agents and their use for promoting the elimination of metallic elements from the body have been the subjects of several excellent reviews.[12, 29, 32, 74, 140, 144, 283, 378, 405] Substances with chelating potentialities are numerous; indeed, chelation is thought to be involved widely as a mechanism of pharmacologic action and in many physiologic processes.[29, 74, 144, 370, 441, 444] However, the number of chelating agents which have been adequately examined pharmacologically and have proved to be

of practical value in the treatment of metal poisonings in man is limited.

Whether a particular metal-binding substance will be therapeutically effective against poisoning with a given metal depends upon the characteristics as well as the concentration and tissue distribution of the metal and upon the nature of the milieu in which the reaction must take place.[74, 223, 282, 372]

One factor is the stability of the complex between metal and chelating agent, which is reflected by the stability constant (K). Table I lists the values of the logarithm of K for a number of ethylenediaminetetraacetic acid*–metal complexes. The greater the value of K, the greater the stability of the metal complex.† From the therapeutic standpoint, the important consideration is not the absolute stability of the metal chelate but rather the *relative* stabilities of the metal and the calcium chelates of EDTA. Since EDTA readily forms complexes with calcium and will thus produce hypocalcemia, its calcium salt is usually employed, except where the chelating agent is being used intentionally to sequester calcium. An ion which forms stronger complexes (has a higher dissociation constant) will displace calcium from the EDTA complex. Thus, from Table I it can be seen that the calcium salt of EDTA would not be expected to chelate strontium or silver effectively but should be very efficient, for example, in chelating trivalent vanadium or iron as well as thorium and mercury in vitro.

While stability of the complex between metal and chelating agent is a *sine qua non* of antidotal effectiveness, a favorable stability constant does not ensure therapeutic usefulness since numerous physiologic phenomena influence the in vivo activity of chelating agents.[223, 372] There are a variety of systems such as plasma and tissue proteins in vivo which may compete with the chelating agent for metal ions with varying degrees of affinity. For example, the relative stability constants for the iron and the calcium chelates of EDTA are highly favorable from the standpoint of possibilities for the removal of iron from the body, but EDTA and some of its structural analogues were unable to remove iron from siderophilin in rabbit serum.[358] The distribution of the metal in the body must also be such that the chelating agent can come in contact with the metal. The metal chelate must, of course, be less toxic than the metal itself; for example, there is suggestive evidence that the complexes of dimercaprol with iron[122] or selenium[47] may be more toxic than the metals themselves. In the final analysis, the therapeutic efficacy of a chelating agent in the treatment of poisoning with a particular metal must be determined in experiments in vivo and by clinical trial.

Table II summarizes the available clinical experiences with the use of the two most extensively studied and utilized chelating agents, dimercaprol (BAL) and edathamil (EDTA). Where clinical evaluation is lacking, seriously limited, controversial, or in conflict with expectations from animal experiments, the information is supplemented with experimental data. The reviews by Stocken and Thompson,[405] Chenoweth,[74] Schubert,[371] and Brieger[49] are extensively referred to in Table II, and references included therein are not generally repeated here. Fig. 1 shows the proposed structures of BAL, EDTA, and penicillamine (see below) and their metal complexes.

***Dimercaprol (BAL).*** BAL is a dithiol, and its sulfhydryl groups compete with sulfhydryl groups of enzymes and other tissue proteins for combination with certain heavy metals (Fig. 1). It is effective, therefore, in antagonizing the actions only of those metals which form mercaptides with essential cellular sulfhydryl groups.[165] BAL is not, for example, an effective antidote against poisoning with selenium,[47] which

*Edathamil or versenate. The calcium-disodium salt is the preparation which is used for the treatment of metal poisoning; sodium salts not chelated with calcium are usually used when chelation of calcium is intended.

†Because these values are logarithmic, a difference of 1 in log K represents a tenfold difference in stability.

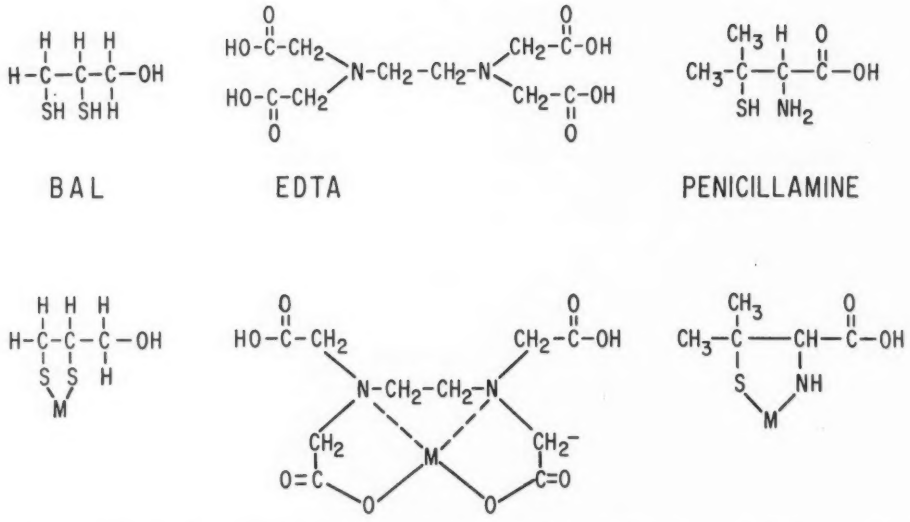



**Fig. 1.** Proposed structures of BAL, EDTA, and penicillamine and, below each, their monomolar complexes with a representative metal, *M*. BAL, and perhaps penicillamine, may also form more stable dimolar complexes with certain metals, i.e., 2M of chelating agent holding the metal ion between them. The EDTA chelate shown here is characteristic of the type formed with a divalent metal such as calcium.

inhibits sulfhydryl enzymes by oxidation, or with uranium,[6, 334, 405] which does not affect sulfhydryl enzymes. BAL seems clearly to be the drug of choice at the present time for the treatment of poisoning by arsenic[49, 405, 426] and mercury.[24, 49, 74, 405] Despite early enthusiasm, it appears to be relatively ineffective and distinctly inferior to EDTA in the treatment of lead poisoning.[29, 32, 49, 74, 341] BAL has generally proved to be ineffective against poisoning with radioactive elements,[6, 240, 334, 371, 405] with the exception of polonium.[212, 371] The place of BAL in the treatment of cadmium poisoning is unsettled at the present time. The administration of BAL to animals with chronic experimental cadmium poisoning has been noted to be associated with severe kidney damage[103, 157]; however, there is suggestive evidence that this difficulty may be circumvented by the use of the more soluble BAL glucoside.[157, 414] The therapeutic status of BAL in relation to other metals is summarized in Table II.

BAL itself is toxic, and its administration in high doses is accompanied by undesirable reactions.[291, 405, 467] Most of the reactions appear to be dose related, occurring in about one-half of subjects receiving 5 mg. per kilogram. Symptoms may appear within 15 to 30 minutes after injection and are usually nausea and vomiting, headache, a burning sensation in the lips, mouth, throat, and eyes, a sense of constriction in the throat and chest, burning and tingling sensations in the extremities and in the penis, lacrimation, salivation, and rhinorrhea, abdominal pain, and a feeling of anxiety and unrest. Children rather frequently develop fever after the second or third injection of BAL, and this may persist until the treatment is discontinued.[467] It has been suggested that the prior administration of ephedrine, diphenhydramine,* or epinephrine may significantly reduce the incidence and severity of the reactions.[199, 423, 426]

Recommended starting doses of BAL are 3 to 5 mg. per kilogram given every 4 to 6 hours by deep intramuscular injection. After the first or second day, the size of the dose and the frequency of administration can usually be reduced. The size of the dose, frequency of administration, and duration of treatment should be deter-

*Benadryl.

mined on the basis of the severity of poisoning and the response of the patient.

***Edathamil calcium-disodium (CaEDTA).*** Edathamil* is one of the most potent chelating agents known. It is capable of forming highly stable, water-soluble metal complexes, and its salts have been used successfully in the treatment of poisoning caused by a variety of heavy metals (Table II). The most extensive therapeutic use of CaEDTA has been in the treatment of lead poisoning, where it has proved to be highly effective and clearly superior to BAL.[29, 49, 56, 74, 341] Reports of the effects of CaEDTA in mercury poisoning are scanty and conflicting[24, 263, 394, 464]; here BAL should probably receive preference at the present time. CaEDTA and related compounds have been used with success to hasten the elimination of a number of radioactive elements, [139, 304, 352, 371, 469] not, however, including strontium.[371, 402] CaEDTA apparently shares with BAL the propensity for forming a nephrotoxic complex with cadmium in chronically poisoned animals[147]; however, it has been reported to have been effective in a few human cases[99] and in acutely poisoned animals.[242, 375, 396] EDTA seems deserving of clinical trial in the treatment of acute iron poisoning in view of the facts that it is effective in enhancing iron excretion in normal human subjects and in patients with iron storage diseases[74, 133, 158, 342] and that it has been noted to reduce serum iron concentrations and prolong the survival of dogs acutely poisoned with ferrous sulfate.[51] The status of EDTA in regard to other metals is summarized in Table II.

EDTA is not metabolized to any appreciable extent,[140] and its principal effects in the body appear to result from its chelating properties. The toxic effects of this compound have been well reviewed by Seven.[377] As mentioned above, the sodium salts of EDTA are capable of chelating calcium, and rapid administration of other than the calcium chelate may result in fatal hypocalcemia. For this reason, the calcium chelate of disodium EDTA is the preparation which is employed in the treatment of metal poisoning. The most serious complication of the use of CaEDTA is the production of renal damage.[53, 113, 140, 141, 192, 377] Severe pathologic changes in the renal tubules, sometimes associated with fatal renal failure, have been noted in both experimental animals and human subjects, and their occurrence appears to be related to the administration of high doses. Thrombophlebitis may result from the intravenous infusion if the concentration of the drug is greater than 0.5 per cent. Occasional systemic reactions have been noted consisting of malaise, fatigue, excessive thirst, numbness, and tingling, followed by sudden fever and shaking chills, myalgia, arthralgia, headache, nausea, and vomiting and occasionally marked urinary frequency and urgency. Histamine-like reactions manifested by sneezing episodes, nasal congestion, and lacrimation sometimes occur. Prolonged administration has been associated with the production of skin and mucous membrane lesions which subside rapidly when treatment is discontinued.

The recommended dosage schedule for CaEDTA is 30 to 50 mg. per kilogram per day given in two divided doses intravenously as a 0.3 to 0.5 per cent solution. Individual treatment courses should be relatively short, preferably no more than 3 days, and should be followed by rest periods of at least 2 days. The total duration of treatment must be determined by the response of the patient.

The oral administration of CaEDTA has been shown to increase the urinary excretion of lead,[45, 390, 395] although the increment is less than that obtained when the drug is administered intravenously, and it is achieved more slowly.[395] However, there is evidence that the increase in lead excretion is due to a transfer of lead from the intestine[341] probably as a result of the formation of a soluble complex. The use of the oral route of administration may, therefore, actually be dangerous. Similarly, the application of edathamil to the contami-

*Versene.

nated skin may solubilize the offending metal and result in increased systemic absorption.[272]

Despite the fact that BAL and the salts of EDTA have proved to be highly effective therapeutic agents, they leave definite deficiencies in the therapeutic armamentarium for metal poisoning and have obvious shortcomings even in those situations where they have been most useful. For example, neither compound will efficiently remove certain radioelements, e.g., strontium, once they have been "fixed" in bone. With regard to EDTA, it would be advantageous to find analogues or even structurally unrelated compounds which have still greater increments of preference for certain toxic metals over calcium. Both BAL and edathamil are toxic, and certainly it would be desirable to improve upon their safety. Finally, both are ineffective orally. For these reasons, extensive efforts are being made to obtain new and better chelating agents. It would be cumbersome and unprofitable to attempt to review all of the numerous studies which have resulted. Brief mention will be made only of a few compounds which have received considerable attention.

***Newer complexing agents.***

*N-Hydroxyethylethylenediaminetriacetic acid.* HEDTA is a structural analogue of EDTA in which one of the acetic acid moieties is substituted by an ethanol group. The log stability constant for its complex with calcium is 8 (for CaEDTA, it is 10.59), but the stabilities of its complexes with a number of metals, e.g., copper, nickel, zinc, and cobalt, are reduced proportionately less by comparison with EDTA.[62] Thus, it has at least the in vitro advantage over EDTA of exhibiting a relatively greater preference for certain metals over calcium. HEDTA bears a close qualitative similarity to EDTA both therapeutically and toxicologically, including, apparently, the propensity for causing renal damage.[377] However its quantitative differences, which have not been fully explored, may provide some therapeutic advantages. For example, HEDTA was found to be more effective than EDTA in promoting the excretion of iron in the same hemochromatotic patient.[223] Like EDTA, HEDTA is capable of inducing hypocalcemia,[377] and for this reason, its calcium chelate is employed therapeutically.

*Diethylenetriaminepentaacetic acid.* DTPA,* while having approximately the same affinity for calcium as EDTA, forms complexes with heavy metals which have stability constants on the order of 100 to 1,000 times greater than those formed by EDTA.[246] Experimentally, DTPA has been found to be more efficient than EDTA in hastening the excretion of lead, cobalt, iron (III), zinc, chromium, yttrium,[140] manganese,[148] and uranium.[61] That this compound may offer particular promise in the treatment of radioelement poisoning is suggested by the fact that it appears to compete favorably with natural binding forces for the "fixed" metal. For example, in chronically poisoned rats, DTPA produced a 45 to 60 per cent reduction in plutonium content of the skeleton as compared with a 10 per cent reduction induced by EDTA.[139] Other workers† have obtained similar results in experimental cerium, yttrium, and plutonium poisoning.[302] A relatively small dose of disodium DTPA (500 mg.) was found to be well tolerated and maximally effective in enhancing yttrium excretion in man.[354] This compound similarly may offer promise in the treatment of iron storage diseases and acute iron poisoning in human subjects. The iron chelate of DTPA is sufficiently stable in vivo that labeled iron administered in this form is excreted almost quantitatively in the urine (in the rat, 92.5 per cent compared with 58.6 per cent for FeEDTA).[359] In addition, there is suggestive evidence that DTPA may be superior to EDTA in enhancing iron excretion in patients with iron storage diseases[128] and that it may be effective in

*Calcium-trisodium DTPA is obtainable for investigational purposes from Geigy Research Laboratories.

†Cited by Foreman.[139]

the treatment of acute iron poisoning.[359] Unfortunately, DTPA shares with EDTA the disadvantages of being poorly absorbed orally and of producing renal damage when given in high doses to experimental animals.[140] However, it is possible that a reduced dose of DTPA, made possible by its increased efficiency, may alleviate this latter difficulty. Like EDTA and HEDTA, DTPA must be given as the calcium chelate to avoid precipitation of hypocalcemia.

*Other EDTA analogues.* Many other interesting and potentially promising variations on the structure of EDTA have been synthesized. A phenolic analogue, ethylenediamine diorthohydroxyphenyl acetic acid (EDDHA) is one of the most powerful known chelating agents for iron (III), its ferric chelate having a stability constant of about 32.[247] Another analogue, 2:2′-bis [di(carboxymethyl)amino]diethyl ether (BAETA), while having approximately the same stability constant for calcium as EDTA, has a higher stability constant for strontium (log = 9.4) than does EDTA (log = 8.6).[401]

The sulfhydryl amino acid, dimethylcysteine or penicillamine, and its derivatives have been found to be effective in promoting the urinary excretion of copper and are used rather extensively now in the treatment of Wilson's disease.[367, 368, 379, 435, 436] This substance, which bears a structural resemblance to BAL (Fig. 1), has also been found to enhance the urinary excretion of lead in patients with plumbism[41, 188] and of iron in patients with iron storage diseases[41, 379] and to protect rats against the lethal effects of mercuric chloride.[13-15]

D-Penicillamine has been found to be less toxic and more effective than the L isomer or the racemic mixture in affording protection against mercury, and *N*-acetyl-D,L-penicillamine has proved to be still more effective and less toxic.[13, 15] Penicillamine is somewhat less active than BAL in protecting against mercury poisoning[13] and than EDTA in promoting the excretion of lead.[188, 293] However, it is possible that this disadvantage may be outweighed by lesser toxicity and ease of administration, since penicillamine and its derivatives can be given orally. The place of these and related compounds in the clinical management of metal poisoning remains to be elucidated fully.

### Narcotic antagonists

Probably the most nearly perfect antidotes available are certain of the *N*-allyl derivatives of narcotic agents, which have proved to be potent inhibitors of the toxic actions of narcotic drugs. The first compound of this type to be studied was *N*-allylnorcodeine, which was reported as early as 1915 to antagonize the respiratory depression induced by morphine.[332] This important observation attracted little notice, however, and a quarter of a century passed before the full therapeutic potential of this phenomenon began to be realized. *N*-allylnormorphine was synthesized in 1942,[440] and extensive pharmacologic studies soon established its abilities to antagonize dramatically many of the effects of morphine in experimental animals.[191, 424] Several years later, its efficacy in counteracting the effects of large doses of a variety of narcotic analgesics in human subjects was demonstrated.[116, 118]

The pharmacology and clinical uses of the narcotic antagonists have been well reviewed by Lasagna,[255] Huggins and Moyer,[209] Woods,[465] Fraser,[142] and Wikler,[445] and the effects of narcotics and antagonists upon respiration and circulation in man have been reviewed recently by Eckenhoff and Oech.[120] The present review will not enumerate all of the works cited in the foregoing. Of the narcotic antagonistic derivatives of analgesics, *N*-allylnormorphine (nalorphine)* and 1,3-hydroxy-*N*-allylmorphinan (levallorphan)† have been the most widely studied and have received the most extensive clinical use. This discussion will be concerned primarily with these two compounds.

*Nalline.
†Lorfan.

Below are listed* analgesic drugs the depressant effects of which are antagonized by nalorphine (and presumably also by levallorphan). Such antagonism is exhibited against a wide variety of natural and synthetic analgesics related pharmacologically to morphine, whether related chemically or not.

Alphaprodine
Anileridine[307, 416]
Codeine (methylmorphine)
Dextromoramide[248]
Dextropropoxyphene† [299, 344]
Dihydromorphinone
Heptazone
Heroin (diacetylmorphine)
Isomethadone
Levorphan
Meperidine
Methadone
Metopon (methyldihydromorphinone)
Morphine
Normethadone‡ [472]
Opium[30]
Oxymorphone[84, 338]
Pantopon
Phenazocine[397]
Piminodine ethanesulfonate[459]
Racemorphan (methorphinan)

Fig. 2 presents the structural formulas for nalorphine, levallorphan, and some potent narcotic analgesics. The structural similarity between the antagonists and morphine is apparent; however, these agents bear only a remote structural resemblance to methadone or meperidine (and its structural analogue, alphaprodine), which they similarly antagonize.

Formulation of a simple mechanistic theory which would reconcile all of the intrinsic pharmacologic properties with the narcotic antagonistic effects of this group of antidotes has met with considerable difficulty. Nalorphine and levallorphan themselves produce effects which are qualitatively similar to those produced by the very drugs which they are capable of antagonizing. In otherwise untreated subjects, they produce sedation and respiratory depression comparable in degree to those produced by morphine[20, 116, 210, 231, 364, 411, 413, 418] and may actually increase the severity of the depressant effects of nonnarcotizing doses of opiates.[20, 209, 317, 411] There is, then, the seeming paradox of the antagonism of depressant drugs by other depressant drugs. The antidepressant actions of nalorphine and levallorphan, for all practical purposes, appear to be restricted to depression produced by narcotics and pharmacologically related analgesics. Most workers have found these agents to be ineffective against the respiratory depression induced by barbiturates, general anesthetics, and similar nonnarcotic central nervous depressants[44, 98, 118, 180, 252, 364]; indeed, as already indicated, they may actually potentiate the depression.[119, 252, 411, 439] A minority of observers have reported that nalorphine counteracts the respiratory depression produced by barbiturates or general anesthetics,[114, 432] but, as pointed out by Woods,[465] this occurred with much larger doses of nalorphine than are required to produce narcotic antagonism and possibly represents a nonspecific effect on respiration which is of no practical significance. The presence of other depressants does not seem to interfere with the action of the antagonists in reversing that amount of depression which is due to narcotics.[117, 286]

Statements have been made to the effect that the antagonists are not universally successful in reversing the depressant effects of narcotic analgesics. However, as is pointed out in the excellent review by Eckenhoff and Oech,[120] the effectiveness of the antagonists appears to be related directly to the magnitude of depression caused by the narcotic, and stimulation of respiration may not occur if the degree of depression is minor. Exceptions to the nearly invariable effectiveness of the antagonists in instances of severe narcotic-induced respiratory depression obviously are to be expected where the depression is complicated by trauma, disease, damage

*From articles cited by Lasagna[255] and/or Woods,[465] except where other references are noted.

†Lilly Research Laboratories: Unpublished data.

‡Levallorphan used.

from hypoxia, or the presence of other drugs.

It is noteworthy that nalorphine does not prevent or abolish the convulsions produced in experimental animals by massive doses of narcotics.[458] Of considerable therapeutic importance is the fact that the narcotic antagonists may precipitate acute abstinence syndromes in patients who are tolerant to narcotics.[143, 229, 446] For this reason, efforts should be made to determine whether or not the patient is an habitual user of narcotics before treatment is instituted. If the tell-tale injection marks and other information suggest that the patient is an addict, treatment with narcotic antagonists must be either avoided or approached with great caution. It is possible, however, to treat such individuals safely[445] if the antagonist is administered very slowly and in amounts just sufficient to improve respirations.

Nalorphine is itself a potent analgesic in man[230, 256] and lacks the addicting potential of the opiates.[142, 216] However, its practical application as an analgesic has been frustrated by cost and the fact that it produces extremely unpleasant side effects, including severe dysphoria and hallucinatory states.[57, 209, 231, 256, 320] The latter observation provides reason also for avoiding overzealous treatment of acute narcotic intoxication with narcotic antagonists.

The effect of the narcotic antagonists in reversing the respiratory depression induced by large doses of morphine and pharmacologically related compounds occurs *pari passu* with a reversal of depressed cerebral oxygen consumption in man.[294] However, the mechanisms whereby these effects are accomplished are not precisely known. Nalorphine penetrates into the brain much more rapidly and in higher concentrations than morphine and likewise has a more rapid rate of egress from the brain.[94] This does not per se explain the antagonistic effects of nalorphine but does explain its rapidity of action as well as the fact that the pharmacologic effects of morphine persist longer than the antagonism afforded by nalorphine.* Nalorphine has been reported to increase the rate of excretion of morphine,[1] but its effect upon the gross concentration of morphine in the brain is not particularly striking and does not appear to offer an explanation of its antagonistic action.[466] A chemical interaction between morphine and the antagonists is unlikely, since this would be expected to result in inhibition of all effects, which does not occur. Moreover, it would not explain the potentiation by nalorphine of the depressant effects of nonnarcotizing doses of morphine.

It has been widely assumed that the narcotic antagonists compete with structurally related drugs for receptor sites in cells (or on enzymes, or in metabolic processes) and that, in essence, the effects of the antagonist are thereby substituted for the effects of the narcotics. The failure to antagonize the effects of therapeutic doses of morphine might be reconcilable with such a theory on the basis that the antagonist has a greater affinity for receptor sites than does the narcotic. This theory postulates, then, that the principal effect which emerges is that of the antagonist, which is less depressant than morphine: when depression is minimal, the substitution of a similarly mild degree of depression would not be discernible, but in major depression, the substitution of minor depression would produce a net improvement. That the antagonists may actually worsen the depression produced by therapeutic doses of morphine is reconcilable with this theory on the basis that a larger total number of receptor sites becomes occupied by one or the other depressant. This theory would also explain the precipitation of abstinence. The finding that nalorphine inhibits the enzymatic demethylation of narcotic drugs[18] strengthens this theory somewhat by suggesting that the antagonist and the narcotic do indeed interact with similar receptor sites, a concept which is supported also by the finding

*The duration of action of single doses of nalorphine is considered to be about 1½ hours and of levallorphan about 2 hours or longer.[120]

that with chronic morphine treatment, there is a parallel reduction in analgesic response and demethylation.[86] However, the observation that the antagonists exhibit stereospecificity with regard to clinical antagonistic effects, but not to inhibition of demethylation,[412] suggests that the similarity between the receptor sites for narcotic action and the receptors for the enzymes that accomplish demethylation may not be as great as had been supposed.

Additional effects produced by narcotic antagonists are difficult to reconcile with the theory of replacement of a potent agent by a less potent one. In man, in contrast to experimental animals, nalorphine appears to be at least as potent an analgesic and respiratory depressant as morphine *(vide supra)*. Nalorphine does not prevent the development of tolerance to morphine[86] or the reduction in activity of demethylating enzymes incident to chronic morphine administration.[229, 274] In certain respects, the two drugs exhibit qualitative as well as quantitative differences in effects. For example, when applied topically to the brain, they act in opposite ways on the thalamic interlaminary system and midbrain reticular formation, which are involved in the organization of consciousness and pain.[153] Differences have also been noted in the action of the two drugs on pulmonary ventilation and blood gas contents[210] and in the subjective effects produced in man.[231] Of great interest, but unclear meaning, are the recent observations* that the respiratory depression produced by nalorphine can be reversed by subsequent treatment with the same drug or levallorphan.

Wikler[446] and Lasagna[255] independently formulated the theory that the antagonistic effects of nalorphine may be dependent on the release of mechanisms responsible for physical dependence. This theory presupposes that physical dependence occurs rapidly and that this is somewhat independent of tolerance. The theory and the available evidence for and against it are well described by Lasagna.[255] In short, it is suggested that "toxic" doses of opiates produce some degree of physical dependence and that antagonism of respiratory depression comes about through an "unmasking" of these effects.

Another theory, also summarized by Lasagna,[255] holds that opiates and pharmacologically related compounds exert both depressive and stimulatory effects, with the former predominating and masking the stimulatory effects. The antagonists are visualized as antagonizing primarily the depressive effects and thereby "unmasking" stimulation by the narcotic drug.

The difficulty of formulating a single hypothesis which would explain all of the available data is apparent. It is unlikely that the exact mechanism of action will be delineated until more precise knowledge of cellular pharmacology is forthcoming.

***Clinical use.*** As mentioned above, nalorphine or levallorphan are almost uniformly effective in overcoming severe respiratory depression produced by large doses of any of the natural or synthetic narcotic analgesics and their pharmacologic analogues. These agents are not, however, effective against depression caused by other sedative agents or pathologic causes and, in fact, may severely potentiate the depression. The narcotic antagonists should be used *only* in the treatment of severe respiratory depression resulting from narcotic analgesics or pharmacologically related compounds. A possible exception is the cautious use of small amounts as a diagnostic test in patients who exhibit severe depression from unknown cause. In this instance, occurrence of improvement is indicative that the coma is due to a narcotic agent; the absence of a response is evidence against such a diagnosis but does not disprove it; particularly if prolonged hypoxia may have been present. Attempts should be made to determine whether or not the patient is a habitual user of narcotics before the narcotic antagonists are administered in order to avoid the precipi-

*A. S. Keats; J. H. Gans; and J. E. Eckenhoff and M. Helrich: Unpublished data cited by Eckenhoff and Oech.[120]

tation of dangerous withdrawal symptoms. Potentially lethal narcotic withdrawal reactions occur also in newborn infants of addicted mothers,[85, 164, 369, 404] and there is at least the theoretic possibility that the situation would be worsened if such an infant were to be given a narcotic antagonist in the treatment of neonatal depression.

In the treatment of severe depression caused by acute narcotic intoxication, the antagonists are usually administered intravenously; the recommended initial doses for adults, children, and newborn infants are listed in Table III. If the initial injection does not produce adequate improvement of pulmonary ventilation within 10 to 15 minutes, one-half to all of the dose may be repeated depending upon the severity of depression. Since the effects of the narcotic may outlast those of the antagonist, the patient should be observed closely for a day or more regardless of the degree of improvement.

The narcotic antagonists, administered either to the mother shortly before delivery or to the infant after birth, have frequently been effective in overcoming neonatal asphyxia caused by narcotic agents administered during labor.[19, 63, 119, 255] It should be emphasized, however, that this form of treatment is not a panacea for asphyxia neonatorum, neither, indeed, is it universally successful or without drawbacks even in those instances in which a narcotic agent can be implicated as a factor contributing to depression. As indicated above, these agents are not effective in antagonizing, and may actually worsen, depression resulting from barbiturates, anesthetic agents or such pathologic causes as brain damage or hypoxia. In this connection, there is the practical problem of assessing the extent to which a narcotic agent administered during labor is contributing to the depression of the infant—an assessment which usually cannot be made with accuracy. If the narcotic is not largely responsible, the antagonists will be ineffective and may worsen the depression. In a large series of newborn infants, it was found, for example, that nalorphine increased the necessity for resuscitation among those whose mothers were subjected to ether anesthesia and that it was relatively ineffective when nitrous oxide was used in conjunction with an opiate.[119] In the same study, there was also suggestive evidence that if nalorphine was administered to the mother too far in advance of delivery (more than 25 minutes), the infants were actually slower in estab-

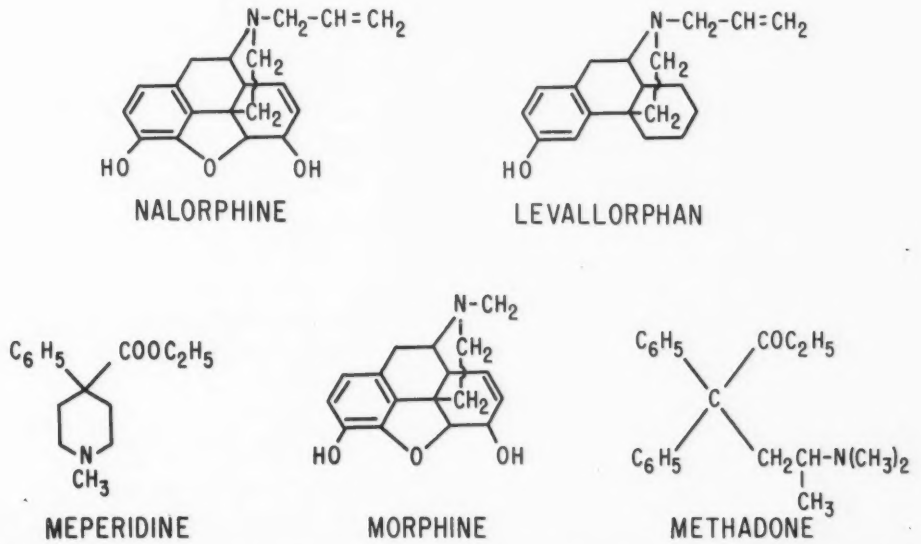



**Fig. 2.** Chemical structures of certain narcotic analgesics and the narcotic antagonists nalorphine and levallorphan.

lishing respiration than were those whose mothers did not receive the drug. Greene[173] wisely discourages the routine use of narcotic antagonists in parturient patients and cautions against the indiscriminate use of narcotics under the cover of antagonists.

### Antidotes for anticholinesterase poisoning

Cholinesterase inhibition is thought to be the principle mechanism involved in the toxic effects of organophosphorus insecticides (e.g., parathion, malathion, Dipterex), the chemical warfare agents known as nerve gases (sarin, tabun, soman), and certain parasympathomimetic drugs including both organophosphorus derivatives (e.g., DFP, TEPP, OMPA) and quaternary or tertiary ammonium compounds (e.g., neostigmine, physostigmine). The pathogenesis and manifestations of poisoning with anticholinesterases have been well reviewed by Koelle and Gilman,[244] Grob and co-workers,[174, 175] and Holmstedt[202]; the latter article is the most extensive recent review of the pharmacology of organophosphorus cholinesterase inhibitors and presents an excellent summary of the pharmacodynamics of these agents.

Acetylcholine is involved in the mediation of ganglionic, neuromuscular, and probably central synaptic nervous transmission. Essential to the neurophysiologic functions of acetylcholine is its rapid subsequent hydrolysis by cholinesterase, a reaction which is inhibited by anticholinesterases as a result of inactivation of the enzyme. The resulting accumulation of acetylcholine at the ends of postganglionic cholinergic nerves causes increased activity of smooth muscle and secretory glands (muscarinic effects); at the neuromuscular junction, it causes muscle weakness and fasciculations (nicotinic effects), and in the central nervous system, anxiety, headache, and in some instances coma and convulsions.

Conventional treatment of anticholinesterase poisoning has consisted of maintenance of a patent airway, artificial respiration when necessary, and the administration of atropine. Large doses of atropine have been shown repeatedly to ameliorate the muscarinic effects and to a lesser extent the central nervous symptoms but to have no appreciable influence on the muscle weakness resulting from neuromuscular block (nicotinic effect). Numerous references to the therapeutic effects of atropine in anticholinesterase poisoning have been cited in the reviews listed previously. Of particular significance in this regard are the demonstration of a markedly increased tolerance for atropine in the presence of anticholinesterase agents and the importance of the early administration of very large doses.[145, 166, 174, 175] Indeed, reviews of reported cases have revealed a direct relationship between survival and the rapidity and intensity of atropinization.[145, 166] Doses of atropine in the range of 2 to 3 mg. are usually well tolerated even in instances of mild anticholinesterase intoxication, and in more severely affected patients, doses of 10 to 20 mg. or more are required to produce maximum benefit. Fortunately, atropine has a relatively wide margin of safety even in the absence of cholinergic stimulation. For this reason, it has been suggested quite appropriately that the consequences of inadequate treatment for anticholinesterase intoxication are to be feared far more than the dangers of overatropinization.[166] The following case typifies the response to

**Table III.** *Suggested initial intravenous doses of narcotic antagonists for the treatment of acute narcotic intoxication*

| *Drug* | *Adults* | *Children* | *Newborn infants* |
|---|---|---|---|
| Nalorphine | 5-10 mg. | 0.1 mg. per Kg. | 0.2-0.4 mg. |
| Levallorphan | 1-2 mg. | 0.02 mg. per Kg. | 0.05-0.1 mg. |

atropine in the presence of moderately severe anticholinesterase poisoning.

A 17-year-old boy ingested an unknown quantity of parathion in a suicide attempt. When seen in the hospital 1 hour later, he was noted to be semicomatose and exhibited marked salivation, lacrimation, sweating, miosis, muscle fasciculations, and evidences of bronchospasm and excessive bronchial secretion. He was given 3 mg. of atropine intravenously over a 20 minute period, and this was followed by marked improvement in all of the above symptoms with the exception of the muscle fasciculations. Over the subsequent 16 hours, he received an additional 2 mg. of atropine in fractional doses, and muscarinic symptoms remained under control. It was only after 8 hours of treatment and 5 mg. total dose of atropine that the pharmacologic effects of atropine per se became apparent.

While atropine occupies a position of great importance in the treatment of anticholinesterase poisoning, its action is one of blocking certain symptoms rather than repair of the defect. In severe anticholinesterase poisoning, death usually occurs as a result of the paralysis of respiratory and pharyngeal muscles, and there has been no practical means of overcoming the underlying neuromuscular block. This has led to a search for more complete antidotes, and considerable attention was given to the theoretic possibility that drugs might be found which would reactivate the inhibited cholinesterase.[453, 454]

It has been found that several nucleophilic agents, notably certain oximes and hydroxamic acid derivatives, are capable of reactivating the inhibited cholinesterase in vitro[28, 77, 92, 136, 177, 196-198, 220, 259, 455, 456] and in vivo.[176-178, 197, 232, 233, 243, 259, 298, 316, 337, 361, 362, 410, 450] These agents have also been shown to protect animals against the lethal effects of anticholinesterases,[16, 17, 21, 28, 52, 90, 106, 115, 136, 198, 235, 236, 239, 259, 365, 450-452, 457] to ameliorate their neuromuscular blocking effects,[21, 176-178, 200, 222, 357, 363, 450] and to retard the development of the electroencephalographic abnormalities which they produce.[264] The question has been raised[52, 121, 197, 357] as to whether the antidotal effectiveness of the oximes is solely dependent upon reactivation of acetylcholinesterase, and resolution of this problem must await further study. Hydroxamic acids have been shown, for example, to accelerate markedly the hydrolysis of certain organophosphorus cholinesterase inhibitors.[184] The structures of some representative members of this class of compounds are illustrated in Fig. 3.

From the practical therapeutic standpoint, it is noteworthy that the oximes, while effective against neuromuscular block, do not strikingly affect the muscarinic manifestations of anticholinesterase poisoning,[176, 177] and it has been a universal finding that the combination of atropine and a cholinesterase regenerator is far more effective than either compound alone.[16, 21, 52, 90, 197, 198, 236, 450, 451, 457] With regard to the effects of oximes on the central nervous manifestations of anticholinesterase poisoning, both theoretic considerations[202] and experimental data[234] suggest that at least one of this group of antidotes (PAM) does not readily penetrate into the brain. However, in cases of human poisoning, administration of this substance has been reported to result in a clearing of consciousness.[227, 298]

Conspicuous among the numerous reports on the antidotal effects of cholinesterase regenerators has been the marked variability of results depending upon the species of experimental animal, the chemical nature of the anticholinesterase, and the time of administration of antidote in relation to poison. Cholinesterase reactivation by oximes has, in general, been found after inhibition by most of the organophosphorus anticholinesterase compounds and, to a less striking degree, by quaternary and tertiary ammonium compounds. There is evidence, however, that the oximes may be relatively ineffective against OMPA, tabun, and dimefox.[9, 123, 232, 236, 365, 457] Parathion poses a problem also in that it is dependent for its toxicity upon metabolic conversion to paraoxon,[202] and because this conversion is slow, it may be necessary to use sustained treatment with oximes to be successful. The negative results in parathion poisoning in some animal experi-

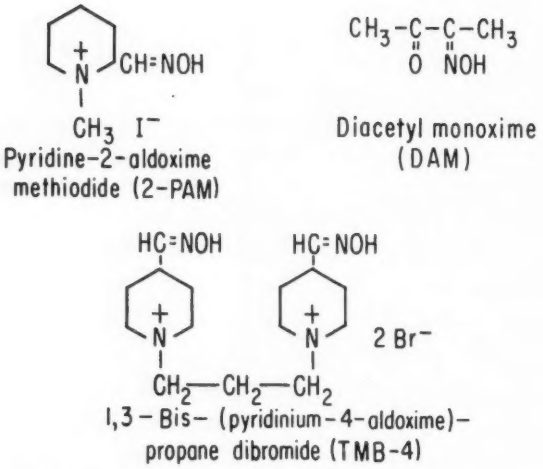



**Fig. 3.** Representative oxime and hydroxamic acid cholinesterase regenerators.

ments[239, 457] may be explainable on this basis. The sustained administration of PAM to humans with parathion poisoning has been successful in relieving symptoms and restoring cholinesterase activity.[298]

The available evidence strongly suggests that inhibition of acetylcholinesterase by organophosphate compounds is more or less irreversible and is based upon phosphorylation of the enzyme.[202] Initially, the complex between inhibitor and enzyme is loose and can be split by reactivators, but after prolonged contact with the inhibitor, the enzyme cannot be reactivated.[196] These observations emphasize the importance of the early administration of the reactivators in the treatment of poisoning caused by organophosphate cholinesterase inhibitors and are in keeping with Erdmann's observation[126] that delayed treatment was relatively ineffective.

***Clinical use.*** Supportive measures are vital adjuncts to the antidotal treatment of anticholinesterase poisoning. It is imperative that any unabsorbed poison be removed. In this regard, it is important to recognize that percutaneous absorption is appreciable with many of the organophosphate compounds and, in fact, is usually the most important route of exposure; hence, thorough cleansing of the contaminated skin is important. If poisoning was by recent ingestion, gastric lavage should be performed. However, if severe symptoms are present, these procedures should await the initiation of antidotal and necessary supportive measures. Airway obstruction is a serious threat to patients with this type of poisoning, because of the excessive pulmonary and oropharyngeal secretions and weakness of pharyngeal muscles. Thus, diligence in removal of secretions and maintenance of a patent airway by endotracheal intubation or tracheostomy, if necessary, are important. Artificial respiration should be instituted if pulmonary ventilation is inadequate.

Available evidence suggests that the combined use of atropine and the cholinesterase regenerators constitutes the antidotal treatment of choice for severe anticholinesterase poisoning. The following suggested regimen represents a composite of the recommendations of several authors.[10, 126, 166, 176, 177, 227, 251, 298]

In the presence of severe poisoning, atropine should be administered intravenously (or intramuscularly if the situation seems less urgent) in a dose of 2 to 4 mg. in adults. Additional doses of 2 mg. should then be administered at intervals of 5 to 30 minutes, depending upon the severity of symptoms and the route of administration, until muscarinic symptoms disappear or the pharmacologic effects of the atropine become apparent. Additional atropine should be given if muscarinic symptoms reappear, and mild atropinization should be maintained for 24 to 48 hours.

The cholinesterase regenerators which have been used most extensively in human cases of poisoning are 2-pyridine aldoxime methiodide (PAM) or methochloride (pralidoxine chloride),* the more soluble methane sulfonate derivative P2S, and diacetyl monoxime (DAM). The most commonly recommended adult dose of these compounds is 1,000 to 2,000 mg., depending upon the severity of poisoning. PAM or

*Protopam chloride, obtainable for investigational use from Campbell Pharmaceuticals, Inc.

P2S can be given intravenously over a period of 5 to 10 minutes, but DAM should be infused one-half to one-third as rapidly. The above doses may be repeated if weakness persists or recurs. Where signs of poisoning tend to persist, maintenance doses may be given either periodically by intramuscular or subcutaneous injection or continuously by slow intravenous infusion.

### Cyanide antidotes

The importance of cyanide as a source of poisoning lies not in the frequency with which it is involved (actually it is a relatively uncommon cause of poisoning) but rather in its extreme toxicity and rapidity of action. Cyanide poisoning represents one of the most urgent of medical emergencies, and the early administration of antidotal treatment is crucial.

Cyanide in various forms is used extensively in metallurgy, in electroplating, in metal cleaning, in the tanning industry, in chemical synthesis and research, and as a fumigant, but the incidence of accidental poisoning from these sources is on the decline. In recent years, the majority of instances of cyanide poisoning have been suicidal, but the current popular sale of cyanide-containing insecticides has introduced a significant accidental poisoning hazard. Cyanogenetic glycosides are present in certain plants, in bitter almonds, and in the seeds of cherry, plum, apricot, and peach, but human cases of poisoning from these sources are extremely rare.

The toxic effects of cyanide are the result of tissue anoxia resulting from reversible inhibition of cellular oxidizing enzymes which contain iron in the ferric state.[165] Of particular importance is the combination of cyanide with cytochrome oxidase,[406] leading to inhibition of cellular respiration. This combination is reversed as cyanide is converted (principally) to thiocyanate through the action of the enzyme rhodanese. Rhodanese seems to be present in tissues in sufficient amounts to permit the conversion of large quantities of cyanide; the limiting factor for the reaction appears to be the availability of thiosulfate.[449] Little rhodanese is present in blood, so that thiocyanate formation is largely limited to that cyanide which is free in tissues.

Methylene blue was proposed many years ago as an antidote against cyanide,[154] and what little activity it had in this regard was attributed to the formation of methemoglobin.[208] Methemoglobin, because its iron content is in the ferric state, competes with cytochrome oxidase for the cyanide ion,[5, 219] and cyanmethemoglobin is formed.[284] Although cyanide ion has a greater affinity for cytochrome oxidase than for methemoglobin, it is possible to produce high circulating levels of the latter, and under these circumstances, there is little formation of the cytochrome oxidase–cyanide complex.[5] Methylene blue is a relatively poor methemoglobin former and, in fact, is of greater value in reversing methemoglobinemia (see the section on toxic methemoglobinemia). A far better methemoglobin former is sodium nitrite,[71] which confers significant protection against the toxic effects of cyanide[71, 290] and restores the diminished oxygen consumption of cyanide-treated animals.[287] Amyl nitrite also affords some protection through methemoglobin formation,[70] but its value is limited by the fact that in man the inhalation of maximally tolerated doses produces only relatively low levels of methemoglobin.[314] *p*-Aminopropiophenone is even more effective than sodium nitrite in promoting the formation of methemoglobin[194, 428] and has been shown to be an effective cyanide antidote.[350] However, methemoglobin formation is somewhat delayed with this compound, and for this reason, it is likely to be of more value as a prophylactic than a therapeutic agent.

Some detoxification of cyanide can be accomplished by augmenting the conversion to thiocyanate through the administration of thiosulfate or donors of colloidal sulfur, with or without the simultaneous administration of the responsible enzyme. Sodium thiosulfate has long been known

to afford some protection against the toxic effects of cyanide.[253] Thiosulfate and rhodanese given together were very active as antidotes in experimental cyanide poisoning.[80] Even more active than thiosulfate in the rhodanese reaction is ethanethiosulfonate, which, when administered together with the enzyme, was a very effective antidote in experimental animals.[81] Mercaptopyruvate can also serve as a sulfur donor in this reaction.[79]

The most useful advance in the treatment of cyanide poisoning came from the demonstration of the synergistic antidotal effects of sulfate donors and compounds which produce methemoglobinemia.[55, 71, 72, 207, 349] The combined use of nitrites and sodium thiosulfate was introduced into clinical therapeutics and popularized by Chen and Rose.[67] This regimen has since been widely employed with impressive success.[68, 69, 73, 215, 333, 462] That the combined use of these agents produces synergistic rather than simply additive effects is apparent from the finding that in cyanide-poisoned dogs, $LD_{50}$ is raised threefold with sodium thiosulfate, fivefold with sodium nitrite, and eighteenfold with the combination of nitrite and thiosulfate.[71] This observation is consonant with the notion (*vide supra*) that methemoglobin completes successfully with cytochrome oxidase for cyanide ion, rendering the latter available for the rhodanese reaction, which is augmented by the provision of its limiting factor, sulfate. The mechanism of poisoning and detoxification can be depicted schematically as follows:

A reversible complex is formed between cyanide and the ferric iron of cytochrome oxidase:

$$\text{Cyt-Fe}^{+++} + \text{CN}^{=} \leftrightarrows \text{Cyt-FeCN}.$$

The administration of nitrite converts the ferrous iron of hemoglobin to the ferric state (methemoglobin):

$$\text{Hgb-Fe}^{++} + \text{NaNO}_2 \leftrightarrows \text{Hgb-Fe}^{+++};$$

the latter competes with ferricytochrome oxidase for cyanide ion, cyanmethemoglobin is formed, and the function of ferricytochrome oxidase is restored:

$$\text{Hgb-Fe}^{+++} + \text{Cyt-FeCN} \rightarrow \text{Hgb-FeCN} + \text{Cyt-Fe}^{+++}.$$

Actual detoxification is then achieved by the reaction of cyanide with thiosulfate to form thiocyanate, which is relatively nontoxic and readily excreted in the urine:

$$\text{Na}_2\text{S}_2\text{O}_3 + \text{NaCN} + \text{O} \underset{\text{SCN oxidase}}{\overset{\text{Rhodanese}}{\rightleftarrows}} \text{NaSCN} + \text{Na}_2\text{SO}_4$$

As is depicted, the latter reaction is slowly reversible through the action of thiocyanate oxidase,[449] and this probably accounts for the recurrence of symptoms of cyanide poisoning which is occasionally seen following antidotal treatment.

The following cases from the author's experience typify the effectiveness of this form of antidotal treatment.

A 61-year-old woman, a chronic alcoholic, ingested with suicidal intent an estimated 5 Gm. of an insecticide powder which contained 42 per cent calcium cyanide (the act was witnessed by her husband). Within approximately 5 minutes, she became semicomatose, irrational, and incontinent of feces. She arrived at the hospital within about 30 minutes and was noted to be irrational, markedly dyspneic, and thrashing about and vomiting occasionally. Blood pressure was 130/70 mm. Hg and pulse 130. Amyl nitrite was administered by inhalation; then sodium nitrite (total dose 0.4 Gm.), followed by sodium thiosulfate (16 Gm.), was given intravenously. Within minutes she became rational, hyperactivity ceased, blood pressure fell to 90/60 mm. Hg, and the pulse rate decreased to 100. Except for the persistence of nausea and vomiting over the next 7 hours, her recovery was uneventful and additional antidotal treatment was not required.

A 38-year-old woman ingested an unknown quantity of an insecticide powder containing 42 per cent calcium cyanide in a suicide attempt. The duration of the interval between ingestion and arrival at the hospital was not known but was though to be less than ½ hour. Upon admission, she was markedly lethargic and dyspneic, the pulse was thready, and blood pressure was 45/0 mm. Hg. She was immediately given 0.45 Gm. of sodium nitrite, followed by 12.5 Gm. of sodium thiosulfate intravenously. This was followed

closely by disappearance of dyspnea, strengthening of the pulse, and increase in blood pressure to 90/70 mm. Hg. The patient opened her eyes and began to converse rationally. The subsequent course was uneventful, and additional antidotal treatment was not required.

A 20-month-old boy was found in the family automobile, crying as if in pain. A partially filled can of a cyanide-containing insecticide was found beside him, and he was covered with the powder. He arrived at the hospital approximately ½ hour later and did not immediately appear ill. Amyl nitrite was administered by inhalation while an intravenous infusion was being prepared. However, before it could be started, he suddenly became comatose. He was given 0.24 Gm. of sodium nitrite, followed by 10 Gm. of sodium thiosulfate intravenously, and showed definite improvement. He then recovered uneventfully without additional antidotal treatment.

Advantage has been taken of metabolic pathways other than the rhodanese reaction in developing antidotes against cyanide. A quantitatively minor pathway of cyanide metabolism involves the formation of cyanocobalamin (vitamin $B_{12}$),[449] and it was thought that the administration of precursors which lack the cyanide moiety might accelerate this reaction and thereby have antidotal value. Both hydroxocobalamin (Vitamin $B_{12a}$)[296, 313] and chlorocobalamin[194] protected experimental animals against the toxic effects of cyanide, and in the case of the former, the urinary excretion of large amounts of cyanocobalamin was shown to occur.[296] Another pathway which was found to exist at least in rats was the detoxification of cyanide by cystine with the formation of 2-imino-4-thiazolidinecarboxylic acid, which is excreted in the urine.[463] Whether these interesting antidotal systems will prove to be of clinical value remains to be determined.

Organic salts of cobalt (gluconate, glutamate, and especially the EDTA chelate) have proved to be highly effective antidotes against cyanide in experimental animals.[312, 315, 449] The exact mechanism of action is not known but may possibly relate to inhibition by cobalt of the enzymatic reduction of methemoglobin.[389] Proceeding on this assumption, it was felt[161] that sodium cobaltinitrite would offer the advantage of being both a former and sustainer of methemoglobin. This substance, given either alone or in combination with thiosulfate, was found to be a more effective antidote than sodium nitrite in experimental animals. Again, the potential practical value of this observation remains to be determined.

***Clinical application.*** At the present time, the antidotal regimen of choice for cyanide poisoning appears to be the combined use of nitrite and thiosulfate* as described by Chen and Rose.[67, 68] Because of the rapidity with which cyanide poisoning may prove fatal, prompt action is a *sine qua non* of its successful treatment. With the Chen and Rose regimen, it is essential that methemoglobin formation be initiated at the earliest possible moment, and such procedures as gastric lavage should either be deferred until this has been accomplished or performed by an assistant so that antidotal treatment is not delayed. Waiting even the amount of time required for the preparation of an intravenous infusion may be undesirable. It is for this reason that the preliminary administration of amyl nitrite by inhalation has been advised.

The recommended procedure is as follows: (1) Perles of amyl nitrite are broken one at a time in a gauze sponge or handkerchief and held under the patient's nose for 15 to 30 seconds each minute until sodium nitrite can be administered. (2) Sodium nitrite (3 per cent solution) is injected intravenously at a rate not in excess of 2.5 to 5 ml. per minute with careful monitoring of the blood pressure during the injection. The usual dose is 10 to 15 ml. for adults; for children, a proportionate dose would be 6 to 8 ml. per square meter of body surface area (e.g., 3 to 4 ml. for the average 2 year old). (3) This is followed with the intravenous injection of sodium thiosulfate in doses of 12.5 Gm.

*A convenient "cyanide antidote package" containing amyl and sodium nitrite, thiosulfate, and excellent instructions for the treatment of cyanide poisoning has been prepared by Eli Lilly & Company.

(50 ml. of a 25 per cent solution). (4) If signs of cyanide poisoning reappear, the sodium nitrite and sodium thiosulfate injections are repeated in one-half of the above doses.

Administration of the antidotes may per se produce alarming symptoms*: Vomiting, syncope, headache, and unconsciousness frequently occur early during the administration of nitrite. Moreover, nitrites are hypotensive agents, and severe hypotension may accompany their administration. For this reason it is desirable that an assistant obtain frequent blood pressure measurements throughout the period that sodium nitrite is being injected; the injection should be interrupted or slowed if a sharp fall in blood pressure occurs. When practicable, it is helpful to have an intravenous infusion of physiologic saline or dextrose solution running during the treatment so that the rate of flow can be increased when necessary to maintain circulatory adequacy. Since the hypotension produced by nitrite is probably related to peripheral pooling of blood,[447] it may be partly overcome by placing the patient in the Trendelenburg position. Hypotension may occur also during the administration of thiosulfate, perhaps because of the formation of thiocyanate, which is well known for its hypotensive properties. One additional note of caution concerns the use of amyl nitrite: continuous inhalation may prevent adequate oxygenation; therefore, there is good reason to utilize the interrupted schedule of administration suggested above.

With this regimen, patients have recovered even when respirations had ceased. For this reason, no case should be considered hopeless until the antidotes have been given a fair trial. Under these circumstances it is necessary, of course, to perform artificial respiration while antidotal therapy is under way.

*The literature unfortunately makes little reference to the appreciable untoward effects of this form of antidotal treatment; consequently, the above statements are drawn principally from the author's experience.

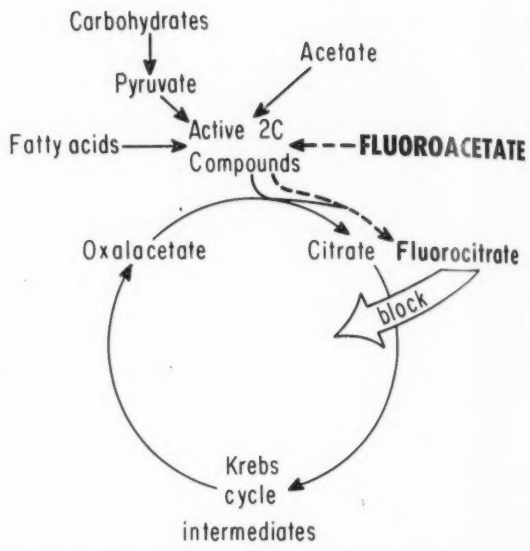



**Fig. 4.** Pathogenesis of the biochemical lesion in fluoroacetate poisoning. (Adapted from Peters.[324])

### Antidotal prospects in fluoroacetate poisoning

Fluoroacetate has long posed a problem in terms of poisoning of livestock, since it is the toxic principle of the plant gifblaar *(Dichapetalum cymosum)*, which grows extensively on the ranges of certain areas of South Africa.[276] Interest in fluoroacetate congeners widened when they gained extensive use as rodenticides. The preparation most commonly used for this purpose at present is sodium fluoroacetate (also known as 1080), which has been involved in a number of cases of poisoning in human beings.[50, 151, 190]

The properties and toxic effects of fluoroacetate have been well reviewed by Chenoweth,[75] Harrison, Ambrus, and Ambrus,[189] Gajdusek and Luther,[151] and Peters,[325] The degree of toxicity and manifestations of intoxication vary widely from one species of animal to another; indeed, the extent of variability exhibited by fluoroacetate is unusual in the annals of toxicology. Also unusual and provocative of much interest and speculation is the latent period between administration of fluoroacetate and the onset of symptoms of poisoning. A latent period of from ½ to 2

hours or more is observed in all species, even after intravenous administration. In the main, the lethal effects of fluoroacetate are related to myocardial and central nervous disturbances, with one or the other predominating depending upon the species of animal. In man, both effects are observed. Nausea and mental apprehension are usually the initial symptoms, followed by epileptiform convulsions. After a period of several hours, pulsus alternans and other disturbances of cardiac rhythm may occur and culminate in ventricular fibrillation and cardiac arrest.

Identification of the biochemical lesion induced by fluoroacetate has contributed an intriguing chapter to the story of pathologic physiology and has provided a fertile field for speculation regarding antidotal possibilities. The numerous investigations on the subject have been well summarized elsewhere.[8, 75, 324-326] In short, the bulk of evidence suggests that fluoroacetate competes with acetate for entrance into the Krebs cycle and is then metabolized to a product which "blocks" the cycle. This process, as visualized by Peters,[324] is depicted in Fig. 4. The presence of fluoroacetate has been shown to lead to the accumulation of citrate in vitro[152, 225, 226] and in vivo,[7, 110, 125, 130, 324, 325, 335] and a product which appears to be a fluorotricarboxylic acid (most likely fluorocitrate or fluoroisocitrate) has been isolated.[124, 328] This product, as well as synthetic fluorocitrate, has been shown to produce citrate accumulation[110, 130, 324, 325] apparently through inhibition of aconitase,[292, 324] the enzyme involved in the metabolism of citrate and isocitrate. There is also evidence that fluoroacetyl coenzyme A is an active intermediate in fluorocitrate synthesis.[277] Thus, it appears that fluoroacetate enters the pool of active two carbon fragments (probably as fluoroacetyl coenzyme A) and is metabolized to fluorocitrate, which in turn blocks the Krebs cycle at the stage of citrate metabolism. Fluoroacetate may operate at other metabolic loci as well, but the above mechanism appears to be the principle determinant of its toxicity. There is suggestive evidence, for example, that fluoroacetate may also be an inhibitor at the acetate stage prior to condensation with oxalacetate.[437]

The net effect of the biochemical alterations produced by fluoroacetate is an accumulation of citrate and fluorocitrate and interference with energy metabolism; however, it is uncertain which of these processes is the primary basis for the various manifestations of fluoroacetate poisoning. Convulsions are rapidly produced in animals by the intracerebral injection of fluorocitrate, but not fluoroacetate.[324] That citrate accumulation per se is not responsible for convulsions is suggested also by the fact that glycerol monoacetate, which is an antidote for fluoroacetate poisoning *(vide infra)* prevents the appearance of convulsions when fluoroacetate is injected into the isolated cerebral cortex but does not prevent the accumulation of citrate.[195] In addition, fluoroacetate-induced or fluorocitrate-induced convulsions, while preceded by citrate accumulation, are not preceded by marked changes in phosphate esters in the brain.[7, 335] The foregoing suggest that the toxicity of fluoroacetate, at least in relation to the brain, is more likely mediated by fluorocitrate formation or interference with energy metabolism than by citrate accumulation; however, the precise mechanism remains unknown.

Sodium acetate antagonizes the effects of fluoroacetate in vitro[75] and in certain species of animals, but not in others.[421] Ethanol likewise has been found to afford some protection,* and its combination with sodium acetate has been found to be more effective than either drug alone.[214, 421] These observations led Chenoweth and coworkers[76] to search for other sources of two carbon moieties which might have practical value as antidotes. The mono-, di-, and triacetate esters of glycerol were studied, and of these, glycerol monoacetate

*Ethanol is metabolized to acetic acid and thereby serves as a source of active two carbon compounds.[449]

(monacetin)* was found to be the least toxic and most effective. Monacetin was able effectively to prevent or reverse both the central nervous and cardiac effects of fluoroacetate in monkeys as well as other experimental animals. Acetamide, the amide of acetic acid, has also been shown to protect rats against fluoroacetate poisoning, but only prior to the accumulation of toxic concentrations of fluorocitrate.[159] Acetate and acetate donors such as acetamide have been shown to inhibit the accumulation of citrate and fluorocitrate.[130, 159, 327]

Though not yet evaluated in man, monacetin at present appears to be the most promising potential antidote for fluoroacetate poisoning and seems deserving of clinical trial. Appropriate doses in man have not been established, but on the basis of monkey experiments, it is suggested[76] that doses in the range of 0.1 to 0.5 ml. per kilogram may be adequate. These doses probably should be repeated hourly for several hours, using the electrocardiogram and the clinical cardiac status as criteria of adequacy of treatment; the appearance of pulsus alternans or electrical alternans should be prevented, if possible. Undesirable side effects of monacetin include sedation, respiratory stimulation, vasodilatation, and local reaction at the site of injection. Some hemolysis may occur, but this has usually not been serious in animal experiments. Deep intramuscular injection would appear to be the route of choice.

### Toxic methemoglobinemia and its treatment

Methemoglobin is an oxidation product of hemoglobin in which the porphyrin iron is converted from the ferrous to the ferric form. It is not capable of transporting oxygen. The problem of methemoglobinemia, its etiology, manifestations, and treatment have been well reviewed by Finch,[134] Bodansky,[35] and Rumler.[360]

Methemoglobinemia can be produced by a wide variety of drugs and intoxicants. Among the drugs and toxic agents which are capable of causing methemoglobinemia are aniline, nitrites, chlorates, phenacetin, acetanilide, sulfonamides, nitrobenzene, quinones, alloxans, and a number of dyes.[35, 134] Nitrates may do likewise through reduction to nitrite. For example, a relatively common cause of methemoglobinemia in small infants is the ingestion of well water containing high concentrations of nitrate.[54, 93, 96, 100, 129, 131, 132, 355, 360] This phenomenon appears to be restricted to infants less than 2 to 3 months of age,[96, 360] and adults have been noted not to develop striking methemoglobinemia despite the fact that infants using the same water supply have been severely involved.[96, 129, 131, 132] The apparent predisposition of young infants may be explainable in part on the basis of a larger intake, per unit weight, of nitrate-contaminated water; however, this does not appear to be the complete answer. The studies of Cornblath and Hartmann[96] indicated that the low gastric acidity of young infants was an important factor in promoting the growth in the upper gastrointestinal tract of microorganisms which are capable of reducing nitrate to nitrite. Another factor which may predispose to the development of methemoglobinemia is the lesser ability of the newborn's erythrocytes to reduce methemoglobin.[355] Cases of nitrate-induced methemoglobinemia have resulted also from the use of bismuth subnitrate in the treatment of infantile diarrhea.[22, 278, 348] The vapor of the diesel fuel additive, amyl nitrate, is an additional potential source of methemoglobinemia.[422]

Because the number of substances capable of producing methemoglobinemia is large and the mode of exposure is often very subtle, this possibility should always be considered in the differential diagnosis of unexplained cyanosis, particularly in infants. Numerous instances can be cited to illustrate the fact that the diagnosis and source of methemoglobinemia may defy

*Monacetin is used commercially in the manufacture of smokeless powder and dynamite, as a solvent for basic dyes, and in tanning. It has moderate narcotic properties in animals.[433]

detection unless the possibility is entertained. Perhaps the best-known case is that of the "11 blue men" who presented at various New York hospitals with unexplained cyanosis and shock. Ingenious investigation disclosed that all of the patients had obtained breakfast in the same cafeteria, where sodium nitrite had inadvertently been substituted for salt in the preparation of oatmeal gruel. The medical details of these cases were reported by Greenberg, Birnkraut, and Schiftner,[172] and the detective work which led to the diagnosis is the subject of a fascinating treatise by Roueche.[356] Tepperman and colleagues[415] described a similar epidemic of methemoglobinemic cyanosis in Syracuse involving 7 persons; the source of poisoning proved to be corning extract which had been inadvertently substituted for maple syrup in a public restaurant. Ten cases of methemoglobinemia occurred in New Orleans as the result of the ingestion of wieners and bologna containing excessive amounts of nitrite.[308] The ingestion of wax crayons has occasionally been responsible for the occurrence of methemoglobinemia in children.[343]

Methemoglobin-producing agents can be absorbed from sites other than the gastrointestinal tract, and this fact adds to the problems which may be encountered in arriving at the correct diagnosis and tracing the source of poisoning. Inhalation and percutaneous absorption have been involved in industrial cases of methemoglobinemia.[273] There are numerous recorded occurrences of epidemics in newborn nurseries of methemoglobinemic cyanosis resulting from the use of diapers freshly stamped with aniline-containing ink; as many as 17,[168] 23,[206] 35,[374] and 41[346] babies have been affected in individual instances. Poisoning has also occurred through the wearing of shoes freshly dyed with aniline-containing pigments.[261, 330] In Egypt, severe methemoglobinemia has occurred in infants following rubbing of the skin with false bitter almond oil as treatment for eczema, diaper rash, and other ailments.[471] Local anesthetics in the "-caine" series have been implicated in the causation of methemoglobinemia after cutaneous application in ointments,[163, 460] rectal administration in suppositories,[329] and local injection for dental extractions.[108] Methemoglobinemia has also resulted from the use of sulfonamide rectal suppositories,[427] and in 1 case involving a nursing infant, it was attributed to the excretion of diphenylhydantoin* in the breast milk.[135]

The physiologic effects of methemoglobinemia are related principally to a reduction in the oxygen-carrying capacity of the blood. However, as in carbon monoxide poisoning, symptoms observed are much more severe than can be accounted for on the basis of the reduction in available oxyhemoglobin. This phenomenon has been attributed to the fact that in the presence of methemoglobin or carboxyhemoglobin, the oxygen dissociation curve of the remaining hemoglobin is shifted in such a manner as to retard the delivery of oxygen to the tissues.[105, 260] Symptoms usually do not appear until 30 per cent or more of hemoglobin pigment has been converted to methemoglobin; 30 to 45 per cent methemoglobinemia is usually associated only with mild symptoms.[36] Oxygenation becomes inadequate when the methemoglobin concentration exceeds about 60 per cent.[35, 273] The lethal concentration in man is estimated to be in excess of 70 per cent, perhaps approaching the lethal level of 80 to 85 per cent for the dog.[36] Chemically induced methemoglobinemia may be associated with hemolysis, but severe hemolytic complications are uncommon.

The presence of methemoglobin in blood can be confirmed by a number of means. A blood specimen containing sizable amounts of methemoglobin or other abnormal intracellular pigments will not exhibit the normal conversion to a bright red color when shaken in the presence of air. Accurate identification of the abnormal pigment can be accomplished by hemoliz-

*Dilantin.

ing a heparinized blood specimen in 10 to 100 volumes of distilled water and subjecting the mixture to spectroscopic examination. If methemoglobin is present, a dark band is observed at 630 mμ; the band disappears with the addition of potassium cyanide, whereas the sulfhemoglobin band at 618 does not.[288] Quantitation can be obtained either by gasometric[430] or colorimetric[127, 205, 211] methods.

***Treatment.*** Methylene blue is highly effective in causing the reduction of methemoglobin,[35, 36, 273, 403, 443, 448] and its position as a useful antidote has been firmly secured. Ascorbic acid is also capable of reducing methemoglobin[156] but not sufficiently rapidly to be of value in the treatment of chemically induced methemoglobinemia.[134]

As mentioned above, difficulty is not usually encountered with methemoglobin levels less than about 60 per cent. Certainly, watchful waiting and supportive treatment will suffice in most instances where the methemoglobin level is below 45 per cent. With levels of greater than 60 per cent or if unconsciousness or other symptoms suggest the presence of uncompensated tissue hypoxia, the administration of methylene blue is probably indicated. The usual dose is 1 to 2 mg. per kilogram given intravenously as a 1 to 2 per cent solution, repeated if necessary within 1 to 2 hours.

Methylene blue itself is moderately toxic, and this fact has caused most workers to reserve its use for those cases in which it is clearly justified. The toxic effects of methylene blue have been summarized elsewhere.[273, 297] The most significant drawback is the possibility of inducing hemolysis, but such a reaction is unlikely with the doses described above.

The following case typifies the antidotal effectiveness of methylene blue.

A 10-year-old girl, apparently suffering reactive depression resulting from the death of her father, ingested an unknown number of analgesic tablets over a 4-day period in a suicide attempt. Some of the tablets contained acetanilide and others acetophenetidin, in addition to caffeine and aspirin. Progressive disorientation, lethargy, and cyanosis were noted beginning the day before admission. An additional large number of pills was taken about 5 hours before admission, and the child's condition rapidly deteriorated. Upon arrival at the hospital she was markedly cyanotic, dyspneic, disoriented, and intermittently semicomatose, and she had a grossly irregular pulse (110 per minute), a blood pressure of 135/80 mm. Hg, rigidity of the extremities, and positive Babinski and Hoffmann reflexes. A blood sample had a dark, chocolate brown color which did not change upon shaking in the presence of oxygen. Her condition did not improve significantly with supportive care including oxygen, so she was given an intravenous injection of methylene blue in a dose of 40 mg. (1.25 mg. per kilogram). Definite improvement was noted within 15 to 20 minutes, and in less than 1 hour all of the above-described abnormal findings had disappeared. Additional treatment with methylene blue was not necessary, and recovery was uneventful.

### A barbiturate antagonist?

The prevalence of barbiturate intoxication has given rise to the hope that an effective antidote will eventually be found. In 1950, Benica and Wilson[25] investigated a series of alkyl derivatives of glutarimide and found them to have convulsant properties. When one of these derivatives, bemegride (β,β-methylethylglutarimide, NP-13, methetharimide),* was subsequently introduced into the treatment of barbiturate intoxication by Shaw and co-workers,[388, 393] it was considered possibly to be a true antagonist.[203, 385, 386, 393] Bemegride bears some structural similarity to the barbiturates and even more so to glutethimide,† which it similarly "antagonizes" (Fig. 5), and this fact suggested the possibility that bemegride may function as a competitive inhibitor of the actions of barbiturates. However, subsequent observations have raised considerable doubt as to the specificity of the bemegride effect.

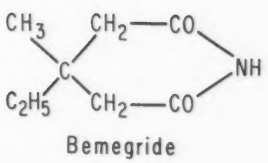
It is abundantly clear that bemegride is a convulsant drug both in animals[25, 40, 66, 238, 306, 376, 387, 470] and human subjects[82, 169, 265, 385] and that its stimulatory effects are exerted against depression induced not

*Megimide, Mikedimide, Eukraton.

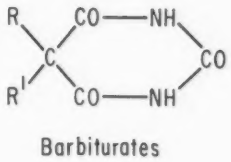
†Doriden.

only by barbiturates but also a wide variety of chemically unrelated depressants.[38, 146, 185, 238, 250, 306, 387, 392, 470] The dose-effect curves for bemegride are similar in slope to the curves obtained with pentylenetetrazol* and picrotoxin in barbiturate-treated animals[238] and human subjects[43] and are similar in animals treated with three different types of depressants—pentobarbital, chloralhydrate, and ethchlorvynol.† These latter findings suggest strongly that the mechanism of action of bemegride in overcoming the depressant effects of barbiturates and chemically unrelated drugs is similar and does not differ from the mechanisms of action of pentylenetetrazol and picrotoxin. Bemegride is thought most closely to resemble pentylenetetrazol pharmacologically.[66, 238, 470] In man, bemegride produces electroencephalographic changes similar to those produced by pentylenetetrazol[169] and in animals the convulsant effects of bemegride are facilitated by reserpine (as is the case with pentylenetetrazol).[66] The analeptic dose-response curve for bemegride is essentially identical with that for pentylenetetrazol.[238]

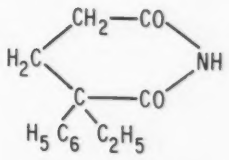
While bemegride is capable of lightening the depth of depression, it does not appear to shorten the duration of coma in patients with severe barbiturate intoxication.[39, 82, 265, 285, 318] In addition, bemegride-treated patients do not awaken with higher blood levels of barbiturate than do controls,[82, 265, 318] as they would be expected to do were bemegride a true competitive antagonist to the barbiturates. Some studies have indicated that bemegride shortens the duration of iatrogenic barbiturate anesthesia,[26, 271, 281, 309, 431, 434] but this has not been confirmed by other workers.[228, 419, 468] These discrepancies may be explicable on the basis of differences in the relative doses of bemegride and barbiturate, the presence or absence of other depressant medications, or the criteria used for identifying termination of anesthesia. In any event,



Bemegride



Barbiturates



Glutethimide

**Fig. 5.** Structures of bemegride, barbiturates, and glutethimide.

the practical usefulness of this procedure seems questionable.

The observation that bemegride alters the tissue distribution of labeled barbiturate in mice[2] requires confirmation. Similar effects have not been found with picrotoxin.[160, 224] Bemegride exerted no effect on the rate of elimination of barbiturate* in poisoned patients.[203, 265, 318]

Not all of the actions of barbiturates are reversed by bemegride. The latter did not antagonize barbiturate-induced depression of respiration in an isolated liver mitochondria preparation[218] or depression of nervous impulse conduction or intestinal motility.[385]

The bulk of available evidence indicates that bemegride is a nonspecific analeptic agent rather than a specific barbiturate antagonist. Similar conclusions have been drawn by other recent reviewers.[185, 187, 262, 340] This does not imply, however, that bemegride does not have a place in the therapeutic armamentarium for barbiturate poisoning. It is a highly potent analeptic drug, and its usefulness (or lack thereof) should probably be adjudged on the same basis as other analeptic agents. Bemegride appears to be more potent as an analeptic than pentylenetetrazol[43, 146, 187, 306, 376] but

*Metrazol.

†Placidyl.

*Caution should be exercised in the conduct of studies of this type, since bemegride may interfere with certain methods for measuring barbiturate concentrations.[101]

less than picrotoxin[258, 306, 376] and perhaps to have a wider margin of safety than either.[187, 376] It may offer the additional advantage over picrotoxin of having a more rapid onset of action,[258, 331] thereby lessening the likelihood of overdosage.

A comprehensive discussion of the pros and cons of analeptic therapy in barbiturate intoxication is beyond the scope of this paper. On the one hand, the followers of Nilsson[301] emphasize supportive care to the exclusion of analeptics,* and on the other, there are those who use (and abuse) analeptic drugs, sometimes, unfortunately, to the exclusion of vital supportive measures. I agree with those who advocate the judicious use of analeptics in occasional, carefully selected patients.[186, 245, 340] Hahn[186] appropriately opines that neither a general rejection of analeptics nor their unlimited application is justified. These drugs should be reserved for patients with extreme intoxication, and their use does not at all diminish the importance of careful supportive care. It should be emphasized also that when analeptic drugs are utilized they should be administered only in amounts sufficient to restore vital reflexes and adequate respiration, and no attempt should be made to arouse the patient.

Of some concern in regard to the use of bemegride are reports of the delayed occurrence of short-lived psychotic reactions after its use in patients with barbiturate intoxication.[82, 241] These have occurred principally in addicts or patients with prolonged unconsciousness and may represent withdrawal reactions.

### Other poisons and antidotes

***Parasympathomimetic agents other than anticholinesterases.*** These include the synthetic choline esters—acetylcholine, carbachol,* methacholine,† and bethanechol‡—and the naturally occurring cholinergic alkaloids—pilocarpine, arecoline, and muscarine. The latter group of substances are toxic constituents of certain plants, but with the exception of the toxic mushrooms *Amanita muscaria* and *A. pantherina* which contain muscarine, these are rare sources of poisoning in this country.§ The choline esters, like the anticholinesterase agents discussed previously, exert both muscarinic and nicotinic effects, while the natural cholinergic alkaloids have only muscarinic properties.[165] Atropine is highly effective in blocking the muscarinic effects of these compounds as well as the anticholinesterases (see "Antidotes for anticholinesterase poisoning") but does not influence the nicotinic effects. Because cholinesterase inhibition does not play a significant role in poisoning with these agents, the "cholinesterase regenerators" are of no value here.

***Fluoride salts.*** These are used commonly as insecticides and as such are important sources of acute poisoning. Soluble fluoride salts are extremely corrosive, and their ingestion is followed by severe hemorrhagic gastroenteritis and sometimes kidney damage. The systemic effects are thought to be related to inhibition of enzymatic activity and to binding of calcium as the insoluble fluoride salt. The extent to which binding of calcium (and perhaps other divalent cations) contributes to the systemic effects of toxic amounts of fluoride is not known. However, the administration of soluble calcium salts (preferably calcium gluconate) is warranted both to correct or prevent hypocalcemia and to inactivate the fluoride.[323]

*In a more recent publication, the "Scandinavian method" of Nilsson and others permits the use of bemegride as a central analeptic in special cases, provided antishock therapy is not thereby neglected. Bemegride is regarded as superior to older analeptics because of the lack of vasopressor, cardiotonic, and hyperpyretic effects.[82a]

†Doryl.

‡Mecholyl.

§Urecholine.

§The Amanita genus of mushrooms also includes *A. phalloides* and the toxicologically identical species *A. brunnescens* and *A. verna,* which produce an entirely different type of poisoning and cause the majority of fatalities from mushroom ingestion. These species exert delayed toxic effects on the gastrointestinal tract, liver, kidney, and heart, and the course is unaffected by atropine. The reader is referred elsewhere for more detailed discussions of mushroom poisoning.[68, 138, 179, 391, 429]

***Polymeric phosphates.*** Sodium hexametaphosphate, sodium tripolyphosphate, and sodium pyrophosphate produce hypocalcemia and metabolic acidosis in experimental animals.[167] Hypocalcemia results from chelation of calcium by the phosphate polymer, and acidosis is thought to result at least in large part from hydrolysis of the polymer to orthophosphoric acid residues. On the basis of these observations, it seems likely that calcium administration may be indicated for the correction or prevention of hypocalcemia in instances of poisoning with these compounds. Whether calcium will have an effect above and beyond correction or prevention of hypocalcemia, i.e., by lessening other aspects of toxicity through formation of the calcium-polymer complex, is speculative. Calcium hexametaphosphate is much less toxic than the sodium salt,[167] but this may be due to the slower absorption of the former or to the prevention of hypocalcemia. A communication from the National Clearinghouse for Poison Control Centers (January, 1958) indicates that among the reports received of ingestions of polymeric phosphates (contained usually in detergents and water softeners), the clinical picture was that of gastrointestinal irritation; hypocalcemia or other systemic manifestations were not apparent. On the other hand, I have observed a child who appeared to be moribund, with profound shock, flaccidity, and irregular bradycardia, after ingestion of sodium hexametaphosphate, who responded dramatically to infusion of calcium gluconate.

***Amphetamine,* dextroamphetamine,† and methamphetamine.*** Central nervous stimulation and hypertension are the most alarming manifestations of acute intoxication with amphetamine and related compounds. Conventional treatment has consisted principally of sedation with barbiturates. It is often difficult, however, to achieve adequate sedation safely, especially in children with severe intoxication. A particularly difficult problem is posed by cases of poisoning involving preparations which combine amphetamine or one of its derivatives with a barbiturate. In such instances, the stimulant effects may predominate early despite the presence of large amounts of barbiturate.

Chlorpromazine has been shown to antagonize the desynchronizing effect of amphetamine on the electroencephalogram of experimental animals.[42, 45] Moreover, chlorpromazine or reserpine in doses which per se were devoid of gross behavioral effects abolished[257] the increase in susceptibility to lethal amphetamine intoxication which is usually observed when mice are subjected to confinement or aggregation.[27, 183] Phenobarbital afforded similar protection, but only in anesthetic doses. These observations prompted the clinical trial of chlorpromazine in the treatment of intoxication caused by amphetamine and related compounds, and the results were gratifying.[112] In a number of children with severe intoxication, the administration of chlorpromazine in ordinary therapeutic doses, e.g., 15 mg. in a two-year-old child, resulted in an immediate and dramatic improvement in the manifestations of central nervous excitation and a gradual return of the blood pressure to normal levels. This form of treatment seems deserving of further trial.

***Phenothiazine "tranquilizers."*** "Extrapyramidal" neuromuscular manifestations have been observed both as untoward reactions to therapeutic administration and as symptoms of acute poisoning with most of the phenothiazine tranquilizers, including chlorpromazine, prochlorperazine, perphenazine, trifluprom azine, mepazine, thiopropazate, fluphenazine, trifluoperazine,* and fluprom azine.†[83, 104, 150, 217, 249, 279, 373, 384, 438]

*Benzedrine.

†Dexedrine.

*Respectively, Thorazine, Compazine, Trilafon, Vesprin, Pacatal, Dartal, Prolixin, Stelazine.

†Although a phenothiazine chemically, promethazine (Phenergan) is dissimilar pharmacologically, being noted primarily for its antihistaminic and sedative properties; the propensity for producing the neuromuscular reaction described above appears to be absent or minimal. Thioridazin (mellaril) apparently is lacking in this property.[149]

The characteristics of this type of reaction have been reviewed elsewhere.[91, 383] The most prominent feature is spasm of voluntary muscles which may vary in severity from mild, often unilateral, spasms of the neck muscles to a "pseudotetanus" picture of opisthotonus, trismus, extensor spasms of the extremities, inability to swallow, and episodic, involuntary shrieking. In the majority of instances, the course, although alarming, is one of uneventful recovery. However, in at least two instances, life-threatening laryngospasm associated with acute respiratory distress has occurred.[78, 438] A number of antiparkinsonian drugs, e.g., benztropine methanesulfonate,* procyclidine,† and ethopropazine,‡[249] as well as caffeine,[162] have been used with some success in the treatment of the reaction. However, with the exception of caffeine, these drugs are not readily available in injectable forms. For this reason and because of the feeling that central ganglioplegic agents seemed to offer "more rational and probably more effective therapy than caffeine against parkinsonism," the antihistamine drug diphenhydramine§‖ was used in the treatment of a severe "extrapyramidal" motor reaction to prochlorperazine.[438] Prompt alleviation of symptoms, including laryngospasm, was achieved. The efficacy of this form of treatment has been confirmed,[345] and a more rapid response has been achieved with diphenhydramine than with caffeine.

***Digitalis.*** The problem of digitalis intoxication and its treatment has been well reviewed recently[399] and will not be discussed in detail. It seems appropriate, however, to enumerate some recent advances which have been made in the quest for antidotes against the toxic effects of digitalis. The value of potassium in the therapy of digitalis intoxication is well established, and the reader is referred to other reviews[88, 266, 399] for a more detailed discussion of this form of treatment. Drawbacks include the occasional aggravation of atrioventricular block and the dangers of inducing potassium intoxication.[399] There is suggestive evidence that the potassium salt of L-glutamic acid may be more effective than other sources of potassium, presumably because of better penetration into cells.[237] Procaine amide* and quinidine have been used with some success in the treatment of arrhythmias of digitalis intoxication, but there is significant danger attendant upon their use.[88]

Calcium enhances the effects of digitalis on the heart, and agents capable of chelating calcium have been used recently in the treatment of arrhythmias caused by digitalis intoxication.[27, 182, 221, 351, 398, 409] The preparations which have been used for this purpose have been the disodium and dipotassium salts of ethylenediaminetetraacetic acid.† This form of treatment has proved to be highly effective in abolishing atrial and ventricular arrhythmias occurring as a manifestation of digitalis toxicity. The effect is not limited to arrhythmias induced by digitalis, since EDTA is capable of suppressing ectopic beats in patients not receiving digitalis.[181, 408] The place of induced hypocalcemia and its value relative to other forms of treatment of digitalis intoxication remains to be defined more fully; however, EDTA appears to offer real promise as an ancillary, if not the principal, therapy at the present time.

An intriguing and potentially promising approach to the antidotal treatment of digitalis intoxication has been the investigation of certain saturated lactones which are themselves devoid of cardiotonic activity but resemble structurally the lactone moi-

*Cogentin.

†Kemadrin.

‡Parsidol.

§Benadryl.

‖A number of antihistamines, including diphenhydramine, promethazine and chlorphenamine are well known for their antiparkinsonian properties which are apparently unrelated to their antihistaminic effects.

*Pronestyl.

†The properties of EDTA and the process of chelation were discussed more fully under "Chelating agents in metal poisoning."

ety of cardiac glycosides.[97] The action of certain cardiac glycosides is thought possibly to depend upon the attachment of the lactone moiety to receptor sites in the myocardium, and it was theorized that competition for such attachment may occur with the structurally related compounds. Whatever the mechanism, the saturated lactones, tetrahydrofurfuryl alcohol and butyrolactone, conferred marked protection against digotoxin toxicity in experimental animals. Further work along these lines certainly seems warranted.

***Antiprothrombin anticoagulants.*** The coumarins—bishydroxycoumarin, cyclocumarol, ethyl biscoumacetate, warfarin, and acenocoumarol*—and the indandione derivatives—phenindione,† diphenadion,‡ and anisindione§—exhibit anticoagulant properties by virtue of inhibiting the production of prothrombin by the liver. With the exception of warfarin, these compounds are rarely involved in poisoning except as a consequence of therapeutic overdosage. Warfarin is used therapeutically as an anticoagulant but additionally enjoys more widespread use than any other substance as a rat and mouse killer. In this form, warfarin has been involved in a number of instances of accidental or suicidal poisoning.[170, 201, 254] The acute toxicity of these agents is low, however, and the dangers of developing hemorrhagic disease as the result of a single ingestion appears to be slight. On the other hand, the repeated ingestion even of small amounts greatly increases the likelihood of developing bleeding complications. For all practical purposes, the mechanism of toxicity of these drugs is related solely to depression of prothrombin production and to its hemorrhagic consequences. The hypoprothrombinemia is effectively counteracted by large doses of vitamin K.[380-382] Vitamin $K_1$ and its oxide are more effective for this purpose than menadione. The recommended dose of vitamin $K_1$ for an adult is 50 to 100 mg. given orally or parenterally. In the event of active hemorrhage, transfusions of fresh whole blood may be lifesaving.

***Bromides.*** Acute bromide intoxication is rare, but chronic bromism is a numerically serious problem. Bromide is excreted by the kidney in the same manner as chloride. Since the kidney attempts to regulate the total halide content of the extracellular fluid but somewhat preferentially reabsorbs bromide and excretes chloride,[37, 461] the intake of large amounts of a bromide salt may result in the displacement of appreciable quantities of chloride. The replacement by bromide of approximately 40 per cent of the chloride content of the extracellular fluid constitutes a potentially life-threatening situation.[165] Increasing the intake of chloride will hasten the elimination of bromide. For this purpose, sodium or ammonium chloride can be given orally or intravenously in amounts which are dependent upon the severity of bromism. The usual dose of supplemental sodium chloride is 6 to 12 Gm. daily in divided doses. Bromide excretion is also augmented by the administration of mercurial diuretics.[37] A reasonable regimen is one in which ammonium chloride is given in a dose of 6 Gm. per day with the intramuscular injection of 2 ml. of meralluride* every second or third day (doses for adults).[213]

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*Respectively, Dicumarol, Cumopyran, Tromexan, Coumadin, and Sintrom.

†Danilone.

‡Dipacin.

§Miradon.

*Mercuhydrin.

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# Vitamin $K_1$ and the vitamin K analogues

*The use of vitamin $K_1$ and various preparations with vitamin K activity in the treatment of hypoprothrombinemic states has long been a well-established procedure. Because the K analogues have often been popularly referred to as vitamin K, confusion has arisen regarding the relationship between these compounds and the true vitamin K. Two types of vitamin K have been found in Nature: vitamin $K_1$, present in various green vegetables, cereals, seeds, tomatoes, and liver, and vitamin $K_2$, isolated from putrefied fish meal. The former has been synthesized and represents the commercially available form of the true vitamin. The K analogues were originally synthesized in an attempt to find compounds with more potent antihemorrhagic activity or substances which could be administered more easily than the early preparations of vitamin $K_1$.*

*This article reviews pertinent aspects of the voluminous literature on vitamin $K_1$ and the K analogues and presents the recorded differences (or similarities) in effectiveness and toxicity between the two types of compounds in various clinical states.*

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In 1931, in a study on the vitamin A and D content of fish meal and meat meal, McFarlane, Graham, and Richardson[68] noted that a high percentage of chicks fed fish meal that had been extracted with ether died of hemorrhage after insertion of the identification bands into the wings. In addition, blood from chicks in this group failed to clot on standing overnight in the laboratory. These occurrences were also observed, but to a lesser extent, in chicks fed meat meal extracted with ether. A diet of untreated meal did not produce these phenomena. In 1933, Holst and Halbrook[54] described hemorrhages and severe anemia in chicks maintained on certain diets. The affected animals could be cured by feeding them small amounts of cabbage. Dam[33] recorded his observation of a new deficiency disease noted in chicks fed an artificial diet. He described extensive internal hemorrhages closely resembling scurvy but unaffected by large doses of vitamin C. Hemorrhages did not occur in chicks fed a diet of cereals or seeds, and Dam concluded that the cause of the disease process must be a deficiency in an antihemorrhagic factor which is present in cereals and seeds and different from vitamin C. Dam[34] subsequently reported that the antihemor-

Received for publication May 24, 1961.

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rhagic factor also could be found in hog liver fat, hemp seed, tomatoes, and kale and suggested that it be called vitamin K.

### Isolation and chemistry

The foregoing observations stimulated considerable activity directed toward isolation of natural vitamin K. In the period 1935-1939, various workers (Almquist and Stokstad,[4] Almquist,[5, 6] Dam,[34] Dam and colleagues,[35] Thayer, Doisy, and associates,[101] and McKee, Doisy, and co-workers[69]) reported the isolation of vitamin K from alfalfa leaf meal (vitamin $K_1$) or putrefied fish meal (vitamin $K_2$). Further research led to the determination of the chemical structure of the naturally occurring K vitamins, synthesis of vitamin $K_1$, and synthesis of numerous quinone compounds with varying degrees of vitamin K activity (Fieser,[43] Fieser and associates,[44] Binkley, Doisy, and colleagues,[18, 19] Almquist and Klose,[7] and Ansbacher and Fernholz[10]).

Vitamin $K_1$ (phytonadione; 2-methyl-3-phytyl-1,4-naphthoquinone) is the only naturally occurring K vitamin available for clinical use. It is a yellow oil, insoluble in water, soluble in fat solvents, stable to air and moisture, but decomposed in sunlight. The synthetic form,* identical in all respects to natural $K_1$, is employed therapeutically, although formerly alfalfa extracts were used. Other quinone compounds, generally designated as K analogues, in common use include (1) menadione (2-methyl-1,4-naphthoquinone), a yellow powder practically insoluble in water, sparingly soluble in alcohol, and decomposed by sunlight, (2) menadione sodium bisulfite† (2-methyl-1,4-naphthoquinone sodium bisulfite), a white powder freely soluble in water, slightly soluble in alcohol, and affected by light, and (3) menadiol sodium diphosphate‡ (2-methyl-1,4-naphthohydroquinone diphosphoric acid ester tetrasodium salt), a white to pink powder very soluble in water and insoluble in alcohol.

### Mechanism of action

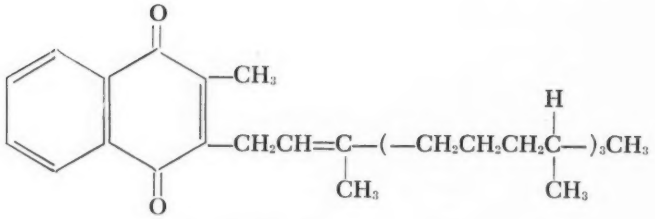
The manner in which vitamin K exerts its effect in the body has been the subject of considerable study, and although significant advances have been made in recent years, the problem is far from settled.

Quick[83] emphasized the importance of vitamin K in the synthesis of prothrombin. He demonstrated that the decrease in prothrombin concentration produced in rabbits by feeding them toxic sweet clover hay and in chicks by placing them on a vitamin K–deficient diet could be prevented in both cases by incorporation of alfalfa in the diet. He suggested that the hemorrhagic diathesis occurring in obstructive jaundice was very likely a manifestation of vitamin K deficiency and that a clinical trial of dietary vitamin K supplementation together with oral bile salts might prove worth while.

In a subsequent article, Quick and Collentine[84] reported on a study designed to determine whether vitamin K is incorporated into the prothrombin molecule or whether it acts in the enzymatic system concerned with the production of prothrombin. Dogs that had been rendered vitamin K deficient by means of cholecystnephrostomy were given intravenous injections of vitamin $K_1$ in a dose of 0.009 mg. per kilogram of body weight (a total of 0.126 mg. for a 14 Kg. dog). This minute quantity restored the prothrombin time from a high of 75 seconds or more to normal (6 seconds) in 4 hours. These findings suggested to Quick and Collentine that vitamin $K_1$, which has a rather large molecular weight, is probably not incorporated directly into prothrombin but combines with an apoenzyme (AE), forming an active enzyme (AE-K) which then is involved in prothrombin synthesis.

In 1941, Campbell and Link[25] isolated from spoiled sweet clover hay the agent

*Mephyton, Konakion.
†Hykinone.
‡Synkayvite.

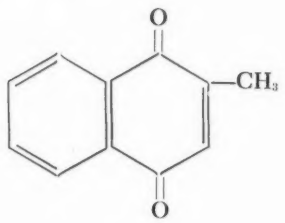


Vitamin $K_1$

responsible for the production of hemorrhagic sweet clover disease in animals. Stahmann, Huebner, and Link[97] identified this compound as 3,3′-methylenebis (4-hydroxycoumarin) and described its synthesis. The substance, commonly called bishydroxycoumarin,* was fed by Overman, Link, and colleagues[78] to rats who had been on a stock diet or a vitamin K–deficient diet. As expected, an increase in prothrombin times and, in some cases, hemorrhages were observed. Hypoprothrombinemia was more severe in rats on a diet deficient in vitamin K. Alfalfa, alfalfa extracts, or vitamin K analogues counteracted the hypoprothrombinemic effect of the anticoagulant.

Many workers have attempted to explain the mechanism involved in the antagonism between bishydroxycoumarin and vitamin K.

Woolley,[111] noting the structural resemblance between the two compounds, suggested the theory of simple competitive inhibition. Collentine and Quick,[26] using dogs with vitamin K deficiency, administered bishydroxycoumarin together with vitamin K and noted little change in prothrombin time at the end of 4 hours. (Vitamin K without the addition of anticoagulant returned the prothrombin time to normal in 4 hours.) Further, the counteracting influence of vitamin K on bishydroxycoumarin was demonstrated by the fact that over a 96 hour period, the prothrombin concentration failed to decrease significantly. These investigators felt that the evidence was strong that vitamin K and bis-



Menadione

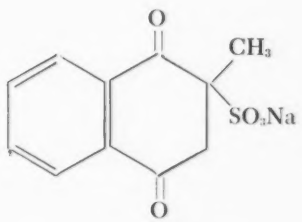
hydroxycoumarin act on the same agent or system. They suggested that the anticoagulant functions as an antivitamin, that it may compete with vitamin K for the apoenzyme with which the vitamin combines for the formation of prothrombin. They also stated that the relative affinity of the vitamin and the anticoagulant for the apoenzyme determines the direction in which the reaction will proceed, and since 0.01 mg. of vitamin $K_1$ counteracted the effect of 1 mg. of bishydroxycoumarin, vitamin K has a greater affinity for the apoenzyme. (The question of affinity might be extended to provide a possible explanation for the greater efficacy of vitamin $K_1$ over the K analogues in combating anticoagulant-induced hypoprothrombinemia.) Collentine and Quick mentioned that when either vitamin K or bishydroxycoumarin has combined with the apoenzyme, an excess of the opposing agent is required to replace the attached component. Babson and associates[16] felt that the vitamin $K_1$–bishydroxycoumarin antagonism is not a simple metabolite-antimetabolite competition. Using rats as the experimental animals, they found that when the ratio of vitamin to anticoagulant is held constant, hypoprothrombinemia reaches a maximum as the dosage is increased. At high doses,

*Dicumarol.

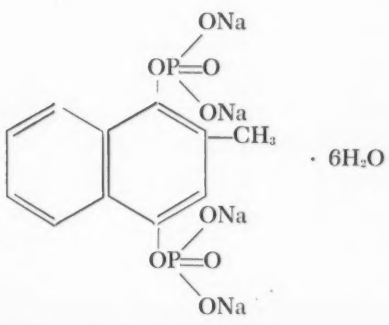
however, the prothrombin level returns to normal, which suggests that at any one level of vitamin $K_1$, a maximum response is achieved and no effect is produced by increasing the bishydroxycoumarin level above that required to reach this maximum.

Lee and co-workers[58] injected a group of mice with $C^{14}$-labeled bishydroxycoumarin and a second group with the radioactive anticoagulant plus menadiol sodium diphosphate and compared the radioactivity in various body tissues. The only significant difference in radioactivity between the two groups occurred in the liver, where, after the first hour following the injection, there was much less radioactivity in the vitamin K–treated mice, suggesting a more rapid displacement of bishydroxycoumarin from the liver in the presence of vitamin K.

Dam and Søndergaard[36] observed that a mixture of plasma from two chicks on a vitamin K–deficient diet produced a prothrombin time somewhere between the values for the individual plasmas alone. This finding also occurred with plasma mixtures from bishydroxycoumarin-treated chicks. However, they observed that a mixture, in certain proportions, of plasma from a chick treated with bishydroxycoumarin and from a chick on a vitamin K–deficient diet produced a prothrombin time which was *less* than that of either plasma alone, provided the difference in prothrombin time of the individual components was not too pronounced. In no instance, however, did a normal prothrombin time result from these mixtures. They postulated that in both the vitamin K–deficient plasma and that with bishydroxycoumarin, there was a diminution of prothrombin, but in addition a second component, unaffected in the K–deficient plasma, was depressed in the bishydroxycoumarin plasma and a third component, unchanged in the bishydroxycoumarin plasma, was decreased in the K–deficient plasma. A detailed discussion of the clotting mechanism is beyond the scope of this review, but it might be mentioned that an abnormal result of a one stage prothrombin time test is observed not only in prothrombin deficiency but also in factor V (labile factor, proaccelerin), factor VII (stable factor, proconvertin), Stuart-Prower factor, and fibrinogen deficiencies. A number of workers, e.g., Lewis and coauthors[59] and Naeye,[77] have demonstrated that both vitamin K deficiency and bishydroxycoumarin therapy result in a decrease in prothrombin and factor VII. In addition, plasma thromboplastin component and plasma thromboplastin antecedent may be diminished. Usually, the labile factor is unaffected in these conditions, but Naeye found a slight reduction in labile factor in some patients with vitamin K deficiency. The increase in both prothrombin and factor VII after vitamin K administration, shown by Lewis and coworkers and Naeye, demonstrates that the vitamin is essential for the formation of factor VII as well as for prothrombin. It appears also to be involved in the production of plasma thromboplastin com-




Menadione sodium bisulfite




Menadiol sodium diphosphate

ponent, plasma thromboplastin antecedent, and the Stuart-Prower factor.[59, 77, 108] It is probable that the experimental findings of Dam and Søndergaard were related to the relative depressions of the clotting factors produced by vitamin K deficiency on the one hand and bishydroxycoumarin administration on the other.

In 1954, Martius and Nitz-Litzow,[63, 64] using liver mitochondrial preparations, implicated vitamin $K_1$ in the mitochondrial oxidative phosphorylation system. This finding represented a significant contribution to the study of the mechanism of action of vitamin K. Martius[65] proposed that vitamin $K_1$ acts between diphosphopyridine nucleotide and cytochrome B (Colpa-Boonstra and Slater[27] disagreed) and suggested that perhaps bishydroxycoumarin uncouples oxidative phosphorylation in the electron transport chain by competitive inhibition of vitamin $K_1$. Cooper and Lehninger[28] observed that bishydroxycoumarin has an uncoupling effect on the phosphorylation coupled to the oxidation of ferrocytochrome C and proposed that the anticoagulant acts at the phosphorylation level and not directly on an electron transport component between diphosphopyridine nucleotide and cytochrome C. Green, Søndergaard, and Dam[52] observed that bishydroxycoumarin added in vitro to liver mitochondria markedly depressed oxidative phosphorylation, but in vivo studies on rats fed the anticoagulant revealed no detectable effect on oxidative phosphorylation. They concluded that bishydroxycoumarin does not exert its therapeutic effect by dissociating oxidation from oxidative phosphorylation but that the toxic effect of the anticoagulant might be based upon that mechanism. Brodie and associates[23] demonstrated that vitamin $K_1$ is involved as a coenzyme in both electron transport and coupled oxidative phosphorylation. Beyer[17] presented data to support this finding. Dallam and Anderson[9, 32] agreed with the finding of Martius and Nitz-Litzow that vitamin $K_1$ participates in respiratory chain phosphorylation, concluding that the vitamin is concerned with either one or both of the phosphorylations occurring between diphosphopyridine nucleotide and cytochrome C.

Quagliariello and associates[82] recently called attention to their studies in vivo and in vitro in which they demonstrated that the natural K vitamins and several K analogues inhibit the synthesis of nicotinic acid at the stage 3-hydroxyanthranilic acid → quinolinic acid. They suggested that the K vitamins exert an antimetabolic effect on 3-hydroxyanthranilic acid.

In the early work with vitamin K and the compounds with vitamin K activity, chick assays were used to compare potencies. Several procedures were employed, the methods of isolation of $K_1$ varied, and some tests employed the alfalfa extract, others the synthetic $K_1$; the results were not uniform. Tishler and Sampson,[104] using the 18 hour test (determination of the clotting time 18 hours after administration of the vitamin to vitamin K–deficient chicks), found that the potency of menadione (administered in oil) was about equal to that of vitamin $K_1$ from alfalfa extract. Ansbacher and associates,[11, 12] employing the 6 hour test, observed that menadione (in oil) was 30 times as active as synthetic vitamin $K_1$ and 4 times as active as alfalfa concentrate. When the test was prolonged to 18 hours, menadione was 4 times as active as both the synthetic and the natural vitamin $K_1$. Menadione in an aqueous medium was twice as active as in oil. This finding is in contrast to that of Dann,[38] who noted that menadione was 3 times as active in an oil medium as in an aqueous medium. Dann employed a 3 day curative technique for biologic assay, stating that the 6 and 18 hour tests are acceptable for determining approximate potencies but are not accurate enough for quantitative work. With the 3 day technique, the activity of menadione (in oil) was about the same as that of the natural vitamin $K_1$ on a molar basis. Thayer and associates[102] in one communication stated that the potency of menadione at 6, 18,

and 72 hours was approximately equal to that of natural vitamin $K_1$. In another article,[103] they called attention to previous studies in which they showed that in the 18 hour test, vitamin $K_1$ is only half as potent as menadione; in the present study, they demonstrated that in the 6 hour test, vitamin $K_1$ administered in 0.1 ml. of oil was one-third as active as menadione but in 0.05 ml. of oil was one-half as active. They felt that in the short-term experiments of 6 hours, the volume of oil might play a role in the absorption of vitamin $K_1$, thus reflecting on the apparent potency.

Foster and co-workers[46] reported on their synthesis and assay of menadiol sodium diphosphate and stated that, when compared on a molecular basis, it is more active than menadione. Ansbacher, Fernholz, and Dolliver[12] disagreed with this. Fieser,[45] in a review article on the chemistry of vitamin K, mentioned that practically every possible modification of the vitamin $K_1$ molecule had been investigated and, with the exception of menadione, each change had resulted in a decrease in biologic potency.

Almquist and Klose[8] reported that menadione has a much greater activity than vitamin $K_1$ and stated that the phytyl side chain detracts from the activity of the 2-methyl-1,4-naphthoquinone nucleus. Fieser,[45] commenting on the finding by some workers of greater potency for menadione, stated that he preferred not to believe that Nature had been outdone. He favored the explanation that the administered menadione becomes involved in a biosynthesis that results in an active compound of the true vitamin type. He postulated that menadione might combine with an alcohol of the phytol or vitamin A type. He further stated that the biosynthesis, which would entail a threefold or fourfold increase in the molecular weight, would explain the supposedly high potency of menadione on a weight basis in the chick assay.

Martius and Nitz-Litzow,[66] using mitochondrial preparations from vitamin K–deficient chicks, observed an increase in oxidative phosphorylation when the medium was made $10^{-5}$M in vitamin $K_1$. A comparable effect was seen with 3-farnesyl-2-methylnaphthoquinone, but menadione was inactive at $10^{-5}$M and inhibitory at $2 \times 10^{-5}$M. They concluded that menadione should be regarded as a provitamin to which a phytyl chain could be added in the body. It is questionable whether the body would be capable of adding a phytyl group, but other long chain, fat-soluble groups, e.g., farnesyl or difarnesyl, might be just as effective in bestowing this type of action to the methylnaphthoquinone nucleus, and they could be added in the body or the gastrointestinal tract.[70] Martius and Nitz-Litzow felt that the vitamin K activity resides in the nucleus but that the side chain binds it to lipoprotein for transport to the site of action.

Quick and Collentine[85] observed in dogs rendered vitamin K deficient by means of cholecystnephrostomy that vitamin $K_1$ was much more effective than menadione in combating hypoprothrombinemia. Since in chicks the two compounds had appeared to be equally potent, or menadione more potent than vitamin $K_1$, they cautioned against attempts to interpret data obtained in lower animals in terms of human metabolism. On the basis of the data then available (1951), they felt that they would not want to decide whether man would react like the dog. The general consensus now is that in both higher animals and man, vitamin $K_1$ is much more reliable than the K analogues in correcting hypoprothrombinemia produced by anticoagulant therapy, but that the K analogues usually are as effective as $K_1$ in combating the hypoprothrombinemia resulting from vitamin K deficiency (see "Comparison of Efficacy"). Miller, Harvey, and Finch,[72] in studies on rats, dogs, and humans who were given vitamin $K_1$ or a water-soluble K analogue together with bishydroxycoumarin, observed a good response to $K_1$ but little or no response to the K analogues.

They commented that since activity on the part of water-soluble K analogues had been noted in assays in vitamin K–deficient birds and animals, the presence of the phytyl chain apparently is not required for prothrombin synthesis in an animal deficient in vitamin K but is necessary in the presence of large amounts of bishydroxycoumarin.

Seeler and associates[90] noted the occurrence of prompt and pronounced hypoprothrombinemia in mice and rats after large doses of 2-sulfanilamidoquinoxaline (sulfaquinoxaline). Vitamin $K_1$ prevented the hypoprothrombinemia if given simultaneously or caused a rapid return of prothrombin concentration to normal if administered after sulfaquinoxaline. In 1947, Mushett and Seeler[75] reported that vitamin $K_1$ was approximately 100 to 250 times more active than menadione, on a weight basis, in preventing sulfaquinoxaline-induced hypoprothrombinemia in rats. (The hypoprothrombinemic effect of sulfaquinoxaline appears within 24 hours, so that inhibition of intestinal bacteria may be discarded as a cause. It is possible that sulfaquinoxaline acts as a vitamin K antagonist.)

### Toxicity studies in animals

Molitor and Robinson[73] conducted toxicity studies in mice, chicks, and rats using phthiocol, menadione, and synthetic vitamin $K_1$. Oral $LD_{50}$ in mice was approximately 0.2 Gm. per kilogram for phthiocol and 0.5 Gm. per kilogram for menadione. Vitamin $K_1$ in doses up to 25 Gm. per kilogram produced no fatalities. Intraperitoneal studies with these compounds (all suspended in sesame oil) revealed a 100 per cent mortality for mice (and close to 100 per cent for chicks) with doses of 0.2 Gm. per kilogram of phthiocol or menadione, but vitamin $K_1$ in doses as high as 25 Gm. per kilogram again failed to cause death. However, the authors pointed out that animals sacrificed 10 days after intraperitoneal injection of vitamin $K_1$ still had considerable amounts of the oily suspension in the abdominal cavity, and they raised the question of whether the apparent lack of toxicity of vitamin $K_1$ was due, in part at least, to a slow rate of absorption. In chronic studies in rats, they noted that daily feeding over a 30 day period of 0.35 Gm. per kilogram of phthiocol and 0.5 Gm. per kilogram of menadione was fatal and that smaller doses of these two drugs (0.1 and 0.35 Gm. per kilogram, respectively) resulted in pronounced anemia. Daily doses of vitamin $K_1$ as high as 2 Gm. per kilogram produced no ill effects.

Ansbacher, Corwin, and Thomas[13] confirmed the findings of Molitor and Robinson in oral acute toxicity studies. Subcutaneous administration of vitamin $K_1$ to mice in doses as high as 6 Gm. per kilogram produced no toxicity, whereas the $LD_{50}$ of menadione was 138 mg. per kilogram. Dogs given three intravenous injections of 5 mg. per kilogram of menadione developed slight anemia but showed no pathologic changes at autopsy. Larger doses of menadione orally (25 to 50 mg. per kilogram per day for 4 to 33 days) also produced anemia, and parenteral doses of the same order of magnitude resulted in addition in hemoglobinuria, urobilinuria, and urobilinogenuria. Similar abnormalities were produced with menadiol dipropionate. Some animals developed an early polycythemia after large doses administered by various routes. Commenting on the wide margin of safety, the authors pointed out that a noninjurious dose of menadione given repeatedly to animals is at least 125 times the maximum clinical dose of 4 mg. for an adult of 150 pounds.

Richards and Shapiro[87] noted methemoglobinemia and cyanosis in dogs given massive but sublethal doses of menadione sodium bisulfite. Those given somewhat lower doses developed *hyper*prothrombinemia on the third day. Postmortem examination revealed hepatic damage. Chronic toxicity studies on dogs given large doses of menadione sodium bisulfite or menadiol sodium diphosphate for 15 days disclosed

an increased urinary urobilinogen level, microscopic hematuria, severe anemia, *hyper*prothrombinemia, and hepatic and renal damage. No evidence of hemolysis was found.

In a recent study by Sunaga, Tadokoro, and Takeuchi,[99] anemia was observed in rats receiving large doses of menadione. Splenomegaly was striking, particularly in the groups administered massive doses. Microscopic examination of the spleen revealed varying degrees of congestion, sinus dilatation, and hemosiderosis. Hepatomegaly with fatty infiltration and enlargement of Kupffer cells was also seen. The kidneys revealed hemosiderin deposits, tubular damage, and interstitial nephritis. To determine whether the spleen played any role in the pharmacologic action of menadione, splenectomized rats were given bishydroxycoumarin and then menadione. There was no interference with the antagonistic effect of the vitamin K analogue.

No fatalities were reported by Dam, Prange, and Søndergaard[36a] after an intravenous injection of 100 mg. per kilogram of vitamin $K_1$ in chicks and rats. There was no mention of signs of toxicity, but this study was designed primarily to determine vitamin $K_1$ concentration in various tissues after large doses.

### Untoward effects in man

Fieser[45] mentioned that those who have worked with menadione and vitamin $K_1$ in the chemical laboratory are aware that the former is a skin irritant while the latter is innocuous. Too rapid intravenous injection of the vitamin $K_1$ emulsion may result in flushing and a sense of constriction in the chest. Rarely, more severe reactions have been noted following $K_1$ injection. Turner[105] reported an instance of transient, severe low back pain and nausea after the intravenous injection of 100 mg. of menadiol sodium diphosphate. This was reproduced with the same dosage on 2 succeeding days, but no symptoms were observed with a 10 mg. dose. The untoward effects of primary concern, however, are those occurring in infants, and in adults with hepatic disease, following large doses of K-type preparations.

***Infants.*** In 1955, Allison[2] called attention to the occurrence of kernicterus and hemolytic anemia in premature infants who had received large doses of menadiol sodium diphosphate for the treatment of hemorrhagic disease of the newborn. Shortly thereafter, Laurance[57] reported an increased incidence of kernicterus in premature infants who had been given the same compound in large doses (30 mg. per day for 3 days).

Bound and Telfer[20] found a higher mean level of plasma bilirubin on the fifth day of life in a group of premature babies who had received 10 mg. per day of menadiol sodium diphosphate for 3 days than in a comparable group of infants who were given only 1 mg. on the first day of life. In the first group, 38 per cent had bilirubin levels of 18 mg. per 100 ml. or higher, while in the second group, only 4 per cent had these levels. (As far as one can assign a figure to represent a dividing line between a dangerous and nondangerous level, 18 mg. per 100 ml. is generally accepted as the point beyond which the occurrence of kernicterus presents a real threat.) Bound and Telfer observed a definite correlation of bilirubin levels with weight in that, in each group, a greater percentage of the smaller babies had concentrations of 18 mg. per 100 ml. or higher than did the heavier infants. In the high dosage group, 2 died of kernicterus and 3 had mild symptoms which might have been due to kernicterus. In the other group, there were no deaths and no symptoms.

Meyer and Angus[71] reported on full-term infants who had received 10 mg. of menadiol sodium diphosphate at birth and on premature babies who were given 10 mg. daily for an average of 3 days. Bilirubin levels were determined in these groups as well as in control groups who had received no therapy. In both full-term and premature infants, the mean bilirubin levels were

significantly higher in the treated than in the control groups. It is known that premature infants, probably because of immature liver function, tend to have higher serum bilirubin levels than full-term babies, and the authors pointed out that the added effect of the water-soluble K analogue may just raise the bilirubin to a level high enough to cause kernicterus.

Lucey and Dolan[60, 61] documented 8 cases of pronounced, early hyperbilirubinemia in newborn infants (7 premature and 1 full-term) whose mothers had received 72 mg. of menadione sodium bisulfite parenterally during labor. The injections had been given 2 to 34 hours prior to delivery, but in one instance, the mother had received the injection 112 hours previously. All the infants were given 2.5 mg. of the compound at birth and another 2.5 mg. on the third day of life. Very high bilirubin levels were noted between 40 and 72 hours after birth. The authors felt that the vitamin K analogue was definitely causative, commenting that ordinarily jaundice of the degree observed does not occur until the fourth to sixth day of life.

Asteriadou-Samartzis and Leikin[15] compared the effect of a water-soluble vitamin K analogue (menadiol sodium diphosphate) with that of vitamin $K_1$ upon the serum bilirubin concentrations of newborn premature infants. The effect of vitamin $K_1$ in full-term infants was also studied. Premature babies who received 30 mg. of menadiol sodium diphosphate over a 3 day period had a higher mean bilirubin concentration (14 mg. per 100 ml.) than a comparable untreated control group (10.03 mg. per 100 ml.). The value for the treated group probably would have been still higher, but 4 had received exchange transfusions prior to the fifth day of life, when all bilirubin determinations applicable to this study were performed in the premature infants. The premature babies who were given 25 mg. of vitamin $K_1$ intravenously on the day of delivery had a mean bilirubin concentration of 6.6 mg. per 100 ml., and those who received 25 mg. orally had a level (10.31 mg. per 100 ml.) approximately equal to that of the control group. Among the full-term control infants, the mean level was 5.07 mg. per 100 ml.; in full-term infants given 25 mg. of $K_1$ intravenously on the first day of life, the value was 3.56 mg. per 100 ml. The authors were gratified to find that in the two groups given vitamin $K_1$ intravenously, the mean bilirubin concentrations were below those of the untreated controls, adding that the 25 mg. dose is at least twice the therapeutic dose and 5 to 10 times the prophylactic dose for hemorrhagic disease of the newborn. However, they also pointed out that among infants weighing less than 1,590 Gm. (3.5 pounds) who received intravenous $K_1$, the mean bilirubin concentration rose above that in the control series, indicating that the 25 mg. dose may be excessive for the smaller infants. In addition, in infants weighing less than 2,500 Gm. (5.5 pounds) who had been given 25 mg. of $K_1$ orally, there appeared to be a tendency to increased bilirubin concentrations as compared with the controls. The latter two observations were based upon very small groups; a much larger series would be required for statistical significance.

The exact mechanism of the toxic effect observed in newborn infants is undecided, but a number of possible explanations have been advanced. Auto-oxidation of certain vitamin K analogues may produce hemolysis in a vitamin E–deficient infant, perhaps by a mechanism similar to that which may prevail in the hemolytic process in vitamin E–deficient animals given alloxan or dialuric acid. Dju, Mason, and Filer[39] found low levels of vitamin E in the tissues and organs of the fetus and premature and full-term infants, apparently because of limited transfer of tocopherol across the placental barrier. Rose and György[88] produced hemolysis in vitamin E–deficient rats by injection of alloxan, alloxantin, dialuric acid, or triketohydrindene hydrate.* No

*Ninhydrin.

hemolysis was observed in tocopherol-treated rats. In vitro studies revealed that dialuric acid and alloxantin (reduction products of alloxan) could hemolyze red blood cells from vitamin E–deficient rats but that alloxan required the presence of reducing agents (cysteine, glutathione, or ascorbic acid) for this effect. Tocopherol added to the reaction mixture protected the cells against hemolysis by dialuric acid. The authors proposed that the hemolysis is linked with the reversible oxidation-reduction system of dialuric acid and alloxan and that the protective action of vitamin E may be best explained as an antioxidant effect.

In a later paper, György, Cogan, and Rose[53] showed that red cells from newborn rats could be hemolyzed by dialuric acid or hydrogen peroxide. It would appear that hydrogen peroxide is involved in the hemolytic process, that it is formed during the oxidation of the unstable reduction product, dialuric acid. The erythrocytes from the mother rats exhibited no hemolysis in the presence of either dialuric acid or hydrogen peroxide. When the red cells of newborn infants were exposed to hydrogen peroxide, hemolysis occurred, but dialuric acid produced no effect. Incubation of the infants' cells with tocopherol rendered them resistant to hemolysis by peroxide. This red cell fragility usually was still present after the fifth day of life, but in infants who had received 50 mg. per day of vitamin E or in infants whose mothers had been given 150 mg. per day during the last weeks of pregnancy, the red cell fragility generally had disappeared by the fifth day of life.

Moore and Sharman[74] and Allison, Moore, and Sharman[3] discussed their findings in vitamin E–deficient rats given various vitamin K analogues or vitamin $K_1$. Rats on a normal diet developed a slight transient decrease in hemoglobin concentration after injection of a massive dose of menadiol sodium diphosphate (100 mg. per kilogram of body weight). Rats on a vitamin E–deficient diet given the same dose showed severe anemia and pronounced hemoglobinuria; the hemolytic effect persisted for several days. No hemoglobinuria occurred in rats deficient in vitamin E given menadiol sodium diphosphate orally in doses as high as 2 Gm. per 100 Gm. diet. Rats on a vitamin E–deficient diet to which supplements of tocopherol had been added showed no adverse effects from injections of the K analogue. In contrast to the findings with menadiol sodium diphosphate, injections of vitamin $K_1$ (100 to 200 mg. per kilogram of body weight) produced no hemoglobinuria in the rats deficient in vitamin E. Menadione sodium bisulfite appeared to be more toxic than menadiol sodium diphosphate, causing hemolysis in the normal as well as the vitamin E–deficient rat. Several other K analogues tested were nontoxic for deficient animals. The authors commented that the chemical nature of menadiol sodium diphosphate suggests that it might be liable to autooxidation and that it might produce hemolysis in the premature vitamin E–deficient infant by a mechanism similar to that which has been postulated for the alloxan derivatives. In vitro studies in which dialuric acid was replaced by menadiol sodium diphosphate in the hemolysis test revealed no effect of the K analogue on red cells from vitamin E–deficient rats. This, of course, does not necessarily rule out the foregoing interesting hypothesis because of the variance between in vivo and in vitro conditions.

The preceding studies are certainly suggestive of a relationship between vitamin K toxicity and vitamin E deficiency, but additional studies are required to elucidate the mechanisms involved.

After the newborn period, Heinz inclusion bodies in red cells do not appear in normal blood.[49] They are associated with hemolytic anemia following exposure to various poisons and drugs. They are also seen in splenic agenesis and after splenectomy. Gasser[49] stated that a slight degree of Heinz body formation is not an abnormal finding in the newborn, particularly in premature infants. He called attention to a re-

port by Willi and Hartmeier[110] in which 18 per cent of newborn infants were described as having Heinz bodies in more than 20 per cent of the red blood cells; 84 per cent of this group were premature babies. Gasser confirmed this finding of spontaneous Heinz body formation, mentioning that it need not be related to increased hemolysis or jaundice and that it disappears within the first few weeks of life. However, he observed 14 cases of hemolytic anemia, icterus, and Heinz body formation occurring in premature infants during the first to third weeks of life. The only common denominator was the administration of menadiol sodium diphosphate, 5 to 10 mg. daily, to all of the infants. Gasser mentioned that a personal communication received from Studer in 1953 reported that 5 mg. of the K analogue produced no Heinz body formation in mice but that 10 mg. caused slight formation and 50 mg. pronounced formation after 14 days. Since then Gasser has used vitamin $K_1$ instead of the water-soluble K analogues for the prophylaxis of hemorrhagic disease of the newborn. However, he stated that he observed hemolytic anemia with Heinz bodies in a premature infant who was given 8 mg. of vitamin $K_1$ between the sixth and twelfth days of life.

Allison[2, 3] found Heinz inclusion bodies in as many as 67 per cent of the circulating red cells in premature infants who developed hemolytic anemia after 30 mg. of menadiol sodium diphosphate daily.

Gasser mentioned that it is not yet apparent why Heinz body anemia resulting from vitamin K therapy occurs only in premature infants. However, the degree of Heinz body formation appears to bear a relationship to the adequacy of hepatic and renal function. These organs play an important role in the neutralization and elimination of toxins, and the functional immaturity in the premature infant may explain the toxic effect of vitamin K.

Certain erythrocyte abnormalities have been observed in patients with drug-induced hemolytic anemia. A low whole blood level of reduced glutathione (GSH), a pronounced decrease in GSH following incubation with acetylphenylhydrazine (GSH stability test), and a deficiency of glucose-6-phosphate dehydrogenase activity have been noted. These defects are genetically determined and have been seen in Negroes and certain ethnic groups.[24, 112] Zinkham[112] pointed out that erythrocytes from a majority of normal newborn babies, both Negro and white, show alterations in GSH metabolism. Whole blood values are similar to or higher than those seen in normal adults, but the result of the GSH stability test is abnormal. This phenomenon is transient, lasting about 1½ to 4 days. During this period, the red cells may be rendered susceptible to hemolysis by vitamin K. Simultaneous GSH determinations and assays for glucose-6-phosphate dehydrogenase activity in the infants revealed that enzyme activity exceeded that noted in normal adults. It would appear that differing mechanisms may be involved in the production of GSH instability in infant red cells and in individuals with drug-induced hemolysis.

Since there is a relationship between the maintenance of a normal level of red cell GSH and the availability and utilization of glucose, Zinkham studied the effect of added glucose on the GSH stability test. The addition of glucose resulted in a much smaller decrease in GSH concentration. It was also observed that the oxidation of GSH by vitamin K could be reversed by adding glucose. The author mentioned that preliminary studies indicated that the insufficient supply of glucose for the GSH stability test was secondary to a low level of blood glucose and an increased rate of glucose utilization by blood of the newborn. However, Zinkham stated that since the amount of glucose required to protect GSH in the GSH stability test is so small, only in unusual circumstances would hypoglycemia play a role in the development of drug-induced hemolysis.

Gottsegen[51] called attention to earlier work in which he and his associates showed

a significant increase in hyperbilirubinemia in the 8 hours after the intravenous injection of 70 mg. of menadiol sodium diphosphate in patients in the acute phase of infectious hepatitis. This effect was not observed in obstructive jaundice and portal cirrhosis. Gottsegen attributed the finding to a temporary, functional overtaxing of the liver's capacity to handle bilirubin and postulated that a similar mechanism might be operative in the premature infant with its immature hepatic function.

Waters and associates,[109] using rat liver extracts and homogenates, observed pronounced inhibition of bilirubin conjugation when menadiol sodium diphosphate was added to the preparations. They concluded that inhibition in vitro occurs at concentrations of the K analogue which might be expected in an infant, particularly after the administration of high doses.

***Adults.*** The administration of large doses of the K analogues or vitamin $K_1$ in an attempt to correct hypoprothrombinemia resulting from hepatic disease has been a widespread practice. It is known that patients with severe liver disease usually will show little or no response to vitamin K, whereas those with mild or moderate involvement may show varying degrees of response, occasionally gratifying in nature (Kark and Souter,[55] Lucia and Aggeler,[62] Seligman and colleagues,[91] Gamble and associates,[48] Pohle and Stewart,[80] Shrifter and Steigmann,[93, 94] Steigmann and coauthors,[98] and Unger, Weiner, and Shapiro[107]). Even when improvement is noted, it generally is gradual, in contrast to the rapid response observed in obstructive jaundice.

Pohle and Stewart[80] studied the effect of vitamin $K_1$ on the prothrombin level of patients with jaundice resulting from liver or biliary tract disease, in most of whom abdominal surgical procedures were eventually performed. Some of the patients had normal, and others increased, prothrombin times. In these two groups, some patients served as controls and the others received 12 to 24 Gm. per day of a cereal plant preparation, together with bile salts. Among those with normal prothrombin levels, no difference was noted in the course of the vitamin K–treated and the untreated groups. Among the patients with hypoprothrombinemia, a good prothrombin response was generally observed in the biliary tract lesions, but there was no response in portal cirrhosis. Some patients with cirrhosis showed a decrease in prothrombin concentration ranging from 10 to 20 per cent, but this may have been within the expected range of fluctuation. A pronounced decrease in prothrombin concentration occurred postoperatively in 3 patients with obstructive biliary cirrhosis, 1 with a common duct stone, and 1 with carcinoma of the head of the pancreas; hemorrhage was noted about 1 to 16 days postoperatively. A postoperative decrease in prothrombin concentration is a not uncommon finding in both jaundiced and nonjaundiced patients. This will be discussed below.

Unger and Shapiro[106] and Unger, Weiner, and Shapiro[107] reported that among patients with liver disease, some with normal prothrombin levels showed a decrease and some with hypoprothrombinemia demonstrated a further depression in prothrombin concentration after large doses of menadiol sodium diphosphate (76 mg. per day intravenously for 4 days). The effect on the prothrombin was transient, lasting about 24 to 48 hours. They postulated that the sudden increase in vitamin K concentration might accelerate the production of prothrombin and that, in the diseased liver, an exhaustion phenomenon might ensue with resultant decrease in prothrombin levels. Shrifter and Steigmann[93, 94] and Steigmann and coauthors[98] reported an increase in hypoprothrombinemia in some patients with hepatic disease after parenteral injection of 72 mg. of menadione sodium bisulfite or 50 mg. of vitamin $K_1$. They cautioned against continuing large daily doses of a K analogue or vitamin $K_1$ in patients with severe liver disease when no significant change in prothrombin con-

centration is observed within 1 to 2 days following the initial dose.

As mentioned above, Gottsegen[51] observed an increase in hyperbilirubinemia in patients with infectious hepatitis following a large dose of menadiol sodium diphosphate intravenously. Recently, Smith and Custer[96] reported the finding of pronounced hypoprothrombinemia and other hepatic function abnormalities postoperatively in an 80-year-old patient who had had abdominoperineal resection for carcinoma of the rectum. They attributed the liver dysfunction to a toxic effect of vitamin K–type preparations given postoperatively. Although this is possible, the evidence presented was not conclusive, as will be seen below. Upon admission, the patient was observed to have a reversal of the albumin: globulin ratio and a prothrombin time of 18 seconds (40 per cent), in the absence of a history of poor nutritional intake. Alkaline phosphatase level was normal on determination. No other liver function tests were performed. Presumably, there was no history of liver disease, and the liver was not enlarged. No vitamin K had been given prior to admission. Two days later, the prothrombin level had risen spontaneously to 69 per cent. On the third day, the patient received 150 mg. of menadiol sodium diphosphate intramuscularly and 50 mg. of vitamin $K_1$ intravenously. Surgical operation was performed on the following day, at which time no gross abnormalities of the liver were noted. For 11 days postoperatively, the patient received 30 mg. of the K analogue daily, and on days 8 through 11, 50 mg. of $K_1$ daily. On the fourth day, postoperatively, the prothrombin activity was 100 per cent, by the seventh had dropped to about 68 per cent, shortly thereafter rose to about 88 per cent, and then dropped precipitously to 29 per cent by the twelfth day postoperatively. At this time, hemorrhagic oozing from the perineum became troublesome and transfusions of fresh blood were given. After several further fluctuations in prothrombin time, a normal level was achieved almost 5 weeks postoperatively. Shortly after the sharp drop in prothrombin concentration was observed, a battery of liver function tests was performed. Most of the test results were abnormal; 18 days later, abnormalities were still evident, but at the end of 28 days, a sulfobromophthalein retention test result was within normal limits. Other liver function tests were not performed at this time. Approximately 4 months postoperatively, repeat liver function tests revealed borderline abnormalities in sulfobromophthalein retention and thymol turbidity. The reversal of the albumin:globulin ratio noted preoperatively was still evident. Prothrombin activity was about 75 per cent.

Smith and Custer contended that the large doses of a K analogue and of vitamin $K_1$ produced a toxic effect upon a patient with a normal liver. Unfortunately, the normalcy of the liver is not well documented since only three tests were performed preoperatively, two of which had abnormal results, although it is recognized that they might not necessarily have been a reflection of hepatic function. As is well known, a normal gross appearance of the liver does not rule out hepatic disease, since pathologic changes have often been found upon microscopic examination of biopsy material from normal-appearing livers (Mateer and colleagues[67]).

There is little doubt, however, that there was some acute process in the liver postoperatively, since a diminution of the abnormalities was subsequently noted. It is also possible that unrecognized preoperative hepatic dysfunction gradually subsided postoperatively. Abels and associates[1] observed a much lower incidence of hepatic abnormalities among patients who had had successful removal of gastrointestinal malignancies 3 months to 10 years previously, as compared to a high incidence of liver dysfunction (in the absence of gross metastases or in the presence of a few small metastases) in patients with gastrointestinal carcinoma; they postulated that the presence of the neoplasm may have been a factor in producing the hepatic dysfunc-

tion. Ariel and Shahon[14] agreed with this view but stated that the liver function abnormalities may, in many cases, result from inanition. Nevertheless, they were able to demonstrate hepatic dysfunction in patients with benign gastrointestinal lesions (mostly peptic ulcer) as well as in those with malignant gastrointestinal disease (rectum, colon, stomach, esophagus) and concluded that the liver dysfunction might be a nonspecific response to gastrointestinal disease. On the other hand, the peptic ulcer or the malignancy might serve as a chronic focus of infection from which bacteria could be disseminated to the liver, or "toxins" might be released into the circulation by the neoplasm. Mateer and associates[67] observed microscopic changes of "acute parenchymal hepatitis" in a patient with peptic ulcer and postulated that organisms from the inflammatory reaction around the ulcer might have been transported to the liver via the portal circulation.

Laying aside the possibility that the patient described by Smith and Custer might have had unrecognized hepatic dysfunction preoperatively which largely subsided after removal of the neoplasm, there is still no conclusive evidence that the vitamin K therapy was the cause of the postoperative disturbance in liver function. Numerous investigators have reported postoperative liver function abnormalities in patients with normal test results preoperatively and increased dysfunction postoperatively in those with liver disease (Fairlie and co-authors,[42] French and co-workers,[47] Geller and Tagnon,[50] Køllgård,[56] Pohle,[81] Schmidt, Unruh, and Chesky,[89] Sims and associates,[95] Tagnon Robbins, and Nichols,[100] Boyce and McFetridge,[21] Boyce,[22] and Cooper and Iob[29]). Abnormalities were noted usually during the first or second day postoperatively, and generally they had subsided by the end of 1 week. In some cases, hepatic dysfunction was still present at the end of 2 to 4 weeks. Frequently, more pronounced postoperative dysfunction was observed in patients with preoperative hepatic abnormalities than in those with normal preoperative function. In addition, those with borderline liver disease were more likely to develop abnormalities than those with a functionally normal liver. Intra-abdominal operations generally were felt to be more likely to result in postoperative hepatic dysfunction than the extra-abdominal types, but there was disagreement in this area, some workers holding the opinion that stress provided by operation was more significant than possible trauma to the liver or bile ducts. Shock, hemorrhage, hypoxia, the nutritional state of the patient, intercurrent infection, duration of anesthesia, and possibly the type of anesthesia have also been implicated in the causation of postoperative liver dysfunction, although not all patients subjected to these conditions will develop abnormalities. These factors will not be discussed in detail here, but it seems worthy of mention that abdominoperineal resection is a traumatic procedure of fairly long duration and that blood loss was apparently a problem in the patient reported by Smith and Custer, since 4,000 ml. of bank blood had been administered postoperatively prior to the precipitous decrease in prothrombin concentration noted on the twelfth day postoperatively. Further studies of liver function in patients receiving large doses of a vitamin K analogue or vitamin $K_1$ would seem to be indicated.

### Comparison of efficacy

As mentioned before, the vitamin K analogues generally are as effective as vitamin $K_1$ in combating hypoprothrombinemia caused by vitamin K deficiency. This, however, is not always the case. Quick and Collentine[84] observed in dogs rendered vitamin K deficient by cholecystnephrostomy, a return of the prothrombin level from below 0.5 per cent to normal 4 hours after the intravenous injection of 9 $\mu$g per kilogram of body weight of vitamin $K_1$; 4 hours after administration of much larger doses of menadione (70 $\mu$g per kilogram of body weight), the prothrombin level was only 40 per cent.

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In instances in which excessive hypoprothrombinemia has been produced by anticoagulant therapy, most investigators agree that vitamin $K_1$ is a more reliable antidote. It is effective against both coumarin and indandione derivatives.

Mushett and Seeler[76] in 1948 observed that vitamin $K_1$ was significantly more effective than menadione in preventing hypoprothrombinemia caused by bishydroxycoumarin in rats and dogs.

Babson and associates[16] found that no amount of menadione would counteract the hypoprothrombinemic effect of 8 mg. of bishydroxycoumarin in rats. Vitamin $K_1$, on the other hand, was very effective. Miller, Harvey, and Finch[72] noted little or no effect of the K analogues given in varying doses (up to 1,000 mg.) to animals and humans who were receiving bishydroxycoumarin; vitamin $K_1$ produced an impressive decrease in prothrombin times. In Miller's studies, the anticoagulant was not discontinued when the vitamin was adminstered. Cromer and Barker[31] gave 64 mg. of menadione sodium bisulfite intravenously to patients with excessive hypoprothrombinemia (over 60 seconds) from bishydroxycoumarin. Most of them demonstrated a decrease in prothrombin time to safe levels within 18 hours. In these patients, the anticoagulant had been discontinued 1 to 2 days prior to administration of the K analogue. Overman, Sorenson, and Wright[79] gave menadione sodium bisulfite or menadiol sodium diphosphate intravenously in doses of 72 to 150 mg. (occasionally more) to patients who had developed excessively prolonged prothrombin times on bishydroxycoumarin therapy. The anticoagulant was omitted on the day of administration of the K analogue, so that in all cases bishydroxycoumarin had not been given for at least 24 hours. The decrease in prothrombin time 24 hours after the K analogue was in most cases greater than in the control series. The responsive patients showed a diminution of 33 to 126 seconds, whereas most of the control group demonstrated a decrease of less than 30 seconds. However, among the group treated with the K analogue, approximately 30 per cent had not yet achieved safe prothrombin levels at the end of 24 hours. Overman, Sorenson, and Wright felt that Miller, Harvey, and Finch probably obtained such poor results with the water-soluble K analogues because their studies were based upon the simultaneous administration of anticoagulant and K analogue, a procedure which would not be expected in the clinical use of the drugs. Miller, Harvey, and Finch were aware that good results with the water-soluble K analogues had been reported, pointing out that they were obtained when the anticoagulant had been discontinued 24 to 48 hours prior to K analogue administration; by the time the latter was given, the body had disposed of most or much of the anticoagulant. Miller, Harvey, and Finch were interested in a rapidly effective antidote in cases of hemorrhage and felt that, aside from blood transfusion, vitamin $K_1$ represented the only reliable treatment.

Douglas and Brown[40] gave patients a single dose of 600 mg. of ethyl biscoumacetate, and although they simultaneously administered 100 mg. of menadiol sodium diphosphate intravenously, they repeated the K analogue injection for the next 2 days. In most patients, there was little or no response to the K analogue, and an essentially similar lack of response was observed when bishydroxycoumarin was employed as the anticoagulant. Since in these patients the last two injections of K analogue were given 24 and 48 hours after the anticoagulant, the theory of Overman and colleagues that the K analogues would be effective if only one were to discontinue the anticoagulant would seem to be contradicted.

Shoshkes, Robins, and Yelin[92] stated that vitamin $K_1$ is more effective than the K analogues in counteracting anticoagulant-induced hypoprothrombinemia but cautioned that patients do not respond identically to a given dose of the vitamin, so that after injection or oral administration, one should not be lulled into believing a safe

prothrombin level automatically will be achieved. Dam and associates[37] also found vitamin $K_1$ to be the most effective antidote and maintained that the K analogues should not be used for the treatment of hemorrhage. They recommended that in cases of serious hemorrhage, an intravenous injection of 10 to 20 mg. of $K_1$ be given, but in the absence of hemorrhage, an excessively prolonged prothrombin time should be treated with small doses of oral $K_1$—2 to 2.5 mg. as a single dose or repeated daily doses of 1 mg. As have other workers, they cautioned against giving excessive doses of vitamin $K_1$, since the patient will be rendered temporarily resistant to renewed anticoagulant therapy, and in addition, bringing the prothrombin concentration up to normal or near normal levels will again expose the patient to the danger of thrombosis. English, Townsend, and Cameron[41] noted a rise in prothrombin concentration in 2 to 3 hours and a safe therapeutic level in 8 to 10 hours after intravenous injection of 5 to 9 mg. of $K_1$ in patients with excessive hyproprothrombinemia from phenylindandione. These doses are above those recommended by Dam but are low in comparison to those employed by some overenthusiastic or overly apprehensive physicians, and even with the 5 to 9 mg. dose, some resistance to reinstituted anticoagulant therapy was encountered. For a period of 2 to 5 days, the $K_1$-treated patients required 2 to 2½ times their usual daily dose of phenylindandione.

Rehbein, Jaretski, and Habif[86] reported that in their clinical experience, the water-soluble K analogues, even in large doses, had proved disappointing in counteracting, rapidly and consistently, excessive anticoagulant-induced hypoprothrombinemia and that they were ineffective in controlling hemorrhage resulting from bishydroxycoumarin therapy. These investigators observed that small intravenous doses (0.5 mg.) of vitamin $K_1$ often were sufficient to treat severe hypoprothrombinemia resulting from hyperresponsiveness to the anticoagulant. When, however, excessive anticoagulant dosage was the cause, higher doses of $K_1$ were required.

Cosgriff[30] administered vitamin $K_1$ orally in doses of 2.5 to 20 mg. (depending upon prothrombin time) to patients with excessively prolonged prothrombin times caused by bishydroxycoumarin or warfarin sodium. In most patients, the prothrombin time decreased to the therapeutic range within 12 hours; in the remainder, safe levels were achieved within 24 hours. In several patients, prothrombin time determinations were performed more frequently in an effort to determine more precisely the latent period between vitamin $K_1$ ingestion and achievement of the desired prothrombin levels. In a few patients, therapeutic levels appeared in 4 to 6 hours, and in the rest, between 8 to 12 hours. Regarding the determination of the proper oral dosage of $K_1$, Cosgriff stated that several factors must be considered: (1) the height of the prothrombin time and the rate at which it is becoming prolonged, (2) the amount and recency of administration of the anticoagulant, and (3) the state of vitamin K stores in the body. To these might be added the presence of minor hemorrhage, in which case somewhat larger doses ordinarily are given than for similar prothrombin levels without hemorrhage. In the presence of moderate or severe bleeding, intravenous therapy should always be employed.

### Conclusions

Vitamin $K_1$ and the vitamin K analogues, when employed judiciously, are valuable preparations in the treatment of various hypoprothrombinemic states. As discussed in the preceding pages, the K analogues are unreliable in anticoagulant-induced hypoprothrombinemia, particularly in emergency states. In portal cirrhosis or other chronic hepatic disease, neither of the two types of preparations may be effective, since the hypoprothrombinemia usually is due predominantly to inability of the liver to form prothrombin rather than to vitamin K deficiency. In biliary cirrhosis, the degree of improvement, if any, in prothrombin

levels after vitamin $K_1$ or K analogue administration is related to the proportion of biliary obstruction to hepatocellular damage. The same premise may be applied to acute hepatic disease, although in this instance, any increase in prothrombin concentration may, in many cases, be due not so much to replacement of vitamin K stores depleted as a result of encroachment on the biliary radicles but rather to a general coincidental improvement in the disease process itself.

The administration of massive doses of the vitamin K analogues to animals has resulted in the production of anemia (hemolytic in some cases), methemoglobinemia and cyanosis, polycythemia, hepatic and renal damage, splenic congestion, and death. There have been fewer published reports on animal toxicity studies with vitamin $K_1$, but they all have demonstrated a lack of toxicity of this compound even in huge doses and even when given to vitamin E–deficient animals.

Since a noninjurious dose of a K analogue given to animals is many times the dose which would be employed clinically in humans (on a weight basis), it would appear that the toxic effects observed in animals with massive doses would be of little concern therapeutically. As has been shown, this is not the case in newborn infants, particularly the premature, and possibly in patients with hepatic disease, in whom undesirable effects occur after doses which have no untoward effects in older children and normal adults. In the latter, doses as high as 200 mg. of menadione and 1,000 mg. of vitamin $K_1$ have produced no evident signs of toxicity.

While it is true that a total dose of 10 mg. or more of a K analogue has resulted in excessive hyperbilirubinemia in newborn infants, the K analogues should not be discarded in the prophylaxis or treatment of hemorrhagic disease of the newborn. Low dosage, e.g., a single injection of 2 mg. of menadione to the mother during labor or 1 mg. to the infant after delivery, or 6 mg. of menadiol sodium diphosphate to the mother or 3 mg. to the infant, is regarded as safe and usually quite effective in physiologic hypoprothrombinemia of the newborn in the absence of hemorrhage. Slightly larger doses are given when hemorrhage has occurred. If vitamin $K_1$ is employed, a dose of 1 to 5 mg. is given orally or parenterally to the mother or infant for prophylaxis and up to 10 mg. (or more, if required) is administered to the infant in cases of hemorrhage. On the whole, perhaps one might feel safer in giving vitamin $K_1$ to the newborn even though, as mentioned above, small doses of the K analogues are regarded as safe, but no definite stand could be taken on this issue without additional studies designed to compare bilirubin levels in newborn infants after small doses of the K analogues and of vitamin $K_1$. It is by no means clear that *large* doses of vitamin $K_1$ will not cause excessive hyperbilirubinemia in infants, but this question is certainly of academic interest only and does not warrant the potential danger to the infant inherent in the administration of excessive doses for experimental purposes.

No definite conclusions can be drawn regarding the mechanism of the toxic effect of various K analogues (and possibly vitamin $K_1$) in the production of excessive hyperbilirubinemia in the newborn. Probably, several factors are involved: (1) A sudden influx of large amounts of K-type preparations in the presence of immature liver function may overwhelm hepatic activity and be reflected principally as an increase in serum bilirubin. (2) The presence of large amounts of a K analogue may inhibit bilirubin conjugation.[109] (3) The K-type preparations may exert a toxic effect on the red blood cells, with production of hemolysis and hyperbilirubinemia. This may be enhanced by or require the presence of (a) vitamin E deficiency, (b) abnormalities in the glutathione metabolism of the erythrocytes, (c) hypoglycemia, or (d) immature hepatic and renal function. (4) Apparently, the chemical nature of the K analogue determines, to some extent at least, its degree

of toxicity, since, as noted previously, Allison, Moore, and Sharman[3] found that certain preparations, e.g., potassium menaphthosulfate and menadoxime, were nontoxic for rats deficient in vitamin E whereas menadiol sodium diphosphate was quite toxic and menadione sodium bisulfite even more so.

An increase in hypoprothrombinemia following large doses of K-type compounds in patients with chronic hepatic disease appears to be a distinct possibility, developing, presumably, as an exhaustion phenomenon in the diseased liver.[106, 107] It is not yet clear whether the preparations can also exert a generalized hepatotoxic effect in these patients.

Finally, the effectiveness of vitamin $K_1$ in combating excessive anticoagulant-induced hypoprothrombinemia has been amply documented in the literature. It cannot be emphasized too strongly that reliance should not be placed upon the K analogues when a rapid increase in prothrombin concentration is desired in an emergency situation arising from anticoagulant therapy.

The assistance of Mrs. Kathleen Casserino and Miss Eleanor Barthelmes in the preparation of this manuscript is gratefully acknowledged.

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# Circulation time: Sodium dehydrocholate versus sodium succinate

## With a case report of a systemic allergic reaction to sodium dehydrocholate

*Circulation times were compared in 50 patients taking sodium dehydrocholate and sodium succinate. Sodium dehydrocholate was found to produce a shorter mean circulation time and less variable results from patient to patient as well as in the same patient. Sodium succinate was found to be safer and somewhat more acceptable to the patient, but its end point was not as sharp as that of sodium dehydrocholate and an end point could not be elicited in some cases.*

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Circulation time is one of the commonly used measures of the circulatory state. A large number of substances have been used to determine circulation time,[5] but the two drugs most frequently used are sodium dehydrocholate* and sodium succinate.† Many investigators have reported on the value of sodium dehydrocholate,[2, 7, 11, 13] but there has been only one published report on sodium succinate,[4] and we have not found in the literature any studies comparing these two agents. Therefore, we undertook to compare sodium dehydrocholate and sodium succinate as measures of circulation time.

Received for publication May 8, 1961.

*Decholin.

†Soduxin.

### Material and methods

The subjects were 50 male and female patients, ranging in age from 15 to 58 years, chosen from the wards of Lincoln Hospital. Postoperative patients and those with heart or lung disease, temperature over 100° F., hemoglobin less than 10 Gm., dehydration, pain, severe apprehension, or dulling of the sensorium were excluded.

After ½ hour of bed rest, while supine, each patient was injected with 5 ml. of 20 per cent sodium dehydrocholate and 1.5 ml. of 30 per cent sodium succinate over a 5 to 10 minute interval. The injections were made with maximum possible speed into the antecubital veins using 5 or 10 ml. syringes and No. 18 or 19 needles. In 25 patients, the paired injections were repeated two to six times at intervals of a few

days. The order of injection was reversed in successive patients and in the repetition of trials in a single patient. The first perception of a bitter taste was taken as the end point for the sodium dehydrocholate method. The end point with sodium succinate was considered to be an involuntary upward movement of the larynx or a cough, whichever came first. Since it was essential that the patient understand the procedure to properly indicate the end point and also that the tester know which end point to look for, both subject and observer were aware of the material used. When perivenous infiltration occurred, the trial was excluded from the tabulation of results because of the uncertain or delayed end point. All tests were performed by the same observer to ensure uniformity of results.

## Results

***Sodium dehydrocholate.*** The results of single 5 ml. intravenous injections of 20 per cent sodium dehydrocholate in 50 patients are summarized in Table I. The results of circulation time determinations with both materials in each of 25 patients are summarized in Table II. All of the patients perceived the bitter taste of sodium dehydrocholate; there were no nonreactors. In 12 of the 93 trials (13 per cent), the subject vomited shortly after the injection. The bitter taste was pronounced in almost all patients, accounting for the sharpness of the end point and for a reluctance of many patients to permit repetition of the test. Inadvertent perivenous infiltration with sodium dehydrocholate at the injection site occurred twice and caused moderate distress for 15 minutes or so, but there was no sloughing or local venous thrombosis. One patient developed an acute systemic allergic reaction to the drug, the details of which are presented in the following brief case report.

*Case report.* The patient was a 54-year-old Puerto Rican man with a 15 year history of intermittent episodes of wheezing and shortness of breath ("asthma") and one allergic reaction to penicillin. At the time of testing, he was free of respiratory symptoms and signs. Intravenously, 5 ml. of sodium dehydrocholate was injected in 2 to 3 seconds, and about 15 seconds later, the patient became nauseated, retched, and vomited several times. After 15 minutes, he developed generalized urticaria, dyspnea, and wheezing. He was given epinephrine intramuscularly, and the symptoms gradually subsided over a period of 2 to 3 hours. Sodium succinate was not tested in this patient.

**Table I.** *Distribution of circulation time scores from patient to patient*

| *Drug* | *No. of patients* | *Trials per patient* | *Circulation time (sec.)* | | |
|---|---|---|---|---|---|
| | | | *Mean* | *Range* | *S.D.* |
| Sodium dehydrocholate | 50 | 1 | 12 | 7-19 | 1.4 |
| Sodium succinate | 50 | 1 | 17 | 6-30 | 5.4 |

$P < 0.00001$.

**Table II.** *Variation of successive circulation time determinations in the same patient*

| *Drug* | *No. of patients* | *Total number of trials* | *No. of trials per patient* | *Difference of successive scores (sec.)* | | |
|---|---|---|---|---|---|---|
| | | | | *Mean* | *Range* | *S.D.* |
| Sodium dehydrocholate | 25 | 93 | 2-6 | 2.1 | 0-7 | 1.8 |
| Sodium succinate | 25 | 87 | 2-6 | 5.1 | 0-12 | 3.8 |

$P < 0.00001$.

**Table III.** *Comparison of 20 per cent sodium dehydrocholate and 30 per cent sodium succinate as measures of circulation time*

| *Criterion* | *Sodium dehydrocholate* | *Sodium succinate* | *Comment* |
|---|---|---|---|
| Mean circulation time | Shorter | Longer | Statistically significant |
| Variation from patient to patient | Less | More | Statistically significant |
| Variation in same patient | Less | More | Statistically significant |
| Frequency of unobtainable end point | Less | More | Data insufficient |
| Sharpness of end point | More | Less | Data insufficient |
| Frequency of vomiting | More | Less | Not statistically significant |
| Frequency of systemic allergic reactions | Occasional | None reported in world literature | Data insufficient |
| Unpleasantness of end point | More | Less | Data insufficient |
| Sloughing and venous thrombosis | None | None | |
| Can be used in comatose and mentally dulled patients and in those with language difficulties | No | Yes | |

***Sodium succinate.*** The results of fifty single 1.5 ml. intravenous injections of 30 per cent sodium succinate in 50 patients are presented in Table I. The results of serial (2 to 6) circulation times performed in each of 25 patients are presented in Table II. The sodium dehydrocholate and sodium succinate values were not infrequently found to vary in opposite directions. In 3 patients, sodium succinate failed to produce an end point. In fifteen trials on 9 patients, the end point was only a mild upward laryngeal movement indistinguishable from an ordinary voluntary swallow. The sharpness of the sodium succinate end point varied considerably from patient to patient and from time to time upon serial testing in the same patient. In five of the eighty-seven trials (6 per cent) with sodium succinate, the patient gagged and vomited because of the pronounced coughing. Inadvertent perivenous infiltration with sodium succinate at the injection site occurred three times and evoked about as much pain as sodium dehydrocholate. There were no instances of sloughing, local venous thrombosis, or allergic reactions.

## Discussion

Table I indicates that the average sodium dehydrocholate circulation time is shorter than that of sodium succinate. Since the circulation time is defined as the *shortest* measurable pathway from vein to artery through the heart and lungs,[5] the method utilizing sodium dehydrocholate is, by definition, a more accurate measure of the circulation time than that with sodium succinate. However, variability of results outranks accuracy in importance.

There are in the literature several reports of systemic allergic reactions to sodium dehydrocholate[1, 3, 6, 8-10, 12] ranging from giant urticaria through asthma and fatal anaphylactic shock. Such reactions have never been reported after sodium succinate.

The authors wish to express their appreciation to Drs. Harry Gold and Dilip Mehta of Cornell University Medical College for their advice in the preparation of this article. We also would like to express appreciation to the Ames Company, Inc., and to the Brewer Company, Inc., for supplying the Decholin and Soduxin used in this study.

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## New information on drugs

### Excerpt from the *Federal Register*

**Substances Generally Recognized as Safe Under the Conditions and With the Limitations Prescribed**

*Lists of substances.*

On February 2 and August 4, 1960, there were published in the FEDERAL REGISTER (25 F.R. 880, 7332) two lists of substances which the Commissioner of Food and Drugs proposed to list in Subpart B . . . as safe for use in foods, subject to the limitations specified. Each of the Commissioner's proposals provided an opportunity for the filing of comments.

After careful consideration of the views and comments filed, some of which are accepted in whole or in part, and some of which are rejected, the Commissioner has concluded that the substances named in the above-cited proposals may properly be added to the list of substances generally recognized as safe. Accordingly, the proposals are adopted as published, except:

1. Minor changes in nomenclature have been made.

2. "Chlorophyll (extracted from plants without change in chemical structure)," under the category "Nutrients," is removed from the list published August 4, 1960, because extraction of chlorophyll from green plant tissues requires a procedure in which it is virtually impossible to remove the chlorophyll in the natural state and thereby permit the addition of chlorophyll per se, to food.

3. Torula yeast, dried, has been removed from the list published February 2, 1960, because the use and processing of "torula yeast, dried" may result in preparations containing a level of folic acid not generally recognized as safe as outlined in the statement of general policy and interpretation on the status of folic acid under the provisions of the Federal Food, Drug, and Cosmetic Act (21 CFR 3.42). Under such conditions, it is concluded that torula yeast, dried, cannot be considered generally recognized as safe as defined in the statute.

It is the opinion of the Commissioner that preparations of yeast, for use in dietary supplements, and which contain folic acid are food additives requiring appropriate regulations prescribing the conditions under which they may be safely used.

These lists are incorporated in § 121.101. *Therefore, it is ordered,* That paragraph (d) of that section be revised to read as set forth below.

This action is taken pursuant to the authority provided in the Federal Food,

Drug, and Cosmetic Act (secs. 409, 701; 52 Stat. 1055, as amended; 72 Stat. 1785; 21 U.S.C. 348, 371) and delegated to the Commissioner by the Secretary of Health, Education, and Welfare (25 F.R. 8625).

*Effective date.* This order shall become effective on the date of publication in the FEDERAL REGISTER.

Dated: January 18, 1961.

GEORGE P. LARRICK,
*Commissioner of Food and Drugs.*

**§ 121.101 Substances generally recognized as safe under the conditions and with the limitations prescribed.**

* * * * * * *

(d) Substances that are generally recognized as safe for their intended use within the meaning of section 409 of the act are as follows:

| *Product* | *Tolerance* | *Limitations or restrictions* |
|---|---|---|
| (1) ANTICAKING AGENTS | | |
| Aluminum calcium silicate | 2 percent. | In table salt. |
| Calcium silicate | 5 percent. | In baking powder. |
| Calcium silicate | 2 percent. | In table salt. |
| Magnesium silicate | 2 percent. | In table salt. |
| *Sodium aluminosilicate (sodium silicoaluminate). | 2 percent. | |
| *Sodium calcium aluminosilicate, hydrated (sodium calcium silicoaluminate). | 2 percent. | |
| Tricalcium silicate | 2 percent. | In table salt. |
| (2) CHEMICAL PRESERVATIVES | | |
| Ascorbic acid | | |
| Ascorbyl palmitate | | |
| Benzoic acid | 0.1 percent. | |
| Butylated hydroxyanisole | Total content of antioxidants not over 0.02 percent of fat or oil content, including essential (volatile) oil content of food. | |
| Butylated hydroxytoluene | Total content of antioxidants not over 0.02 percent of fat or oil content, including essential (volatile) oil content of food. | |
| Calcium ascorbate | | |
| Calcium propionate | | |
| *Calcium sorbate | | |
| Caprylic acid | | In cheese wraps. |
| Dilauryl thiodipropionate | Total content of antioxidants not over 0.02 percent of fat or oil content, including essential (volatile) oil content of the food. | |
| Erythorbic acid | | |
| Gum guaiac | 0.1 percent (equivalent antioxidant activity 0.01 percent). | In edible fats or oils. |

*Substances added from February 2 and August 4, 1960, proposed lists.

| *Product* | *Tolerance* | *Limitations or restrictions* |
|---|---|---|
| (2) CHEMICAL PRESERVATIVES —cont'd | | |
| Methylparaben (methyl-*p*-hydroxybenzoate). | 0.1 percent. | |
| Nordihydroguaiaretic acid | Total content of antioxidants not over 0.02 percent of fat or oil content, including essential (volatile) oil content of the food. | |
| Potassium bisulfite | | Not in meats or in food recognized as source of vitamin $B_1$. |
| Potassium metabisulfite | | Not in meats or in food recognized as source of vitamin $B_1$. |
| Potassium sorbate | | |
| Propionic acid | | |
| Propyl gallate | Total content of antioxidants not over 0.02 per cent of fat or oil content, including essential (volatile) oil content of the food. | |
| *Propylparaben (propyl-*p*-hydroxybenzoate). | 0.1 percent. | |
| Sodium ascorbate | | |
| Sodium benzoate | 0.1 percent. | |
| Sodium bisulfite | | Not in meats or in foods recognized as a source of vitamin $B_1$. |
| Sodium metabisulfite | | Not in meats or in foods recognized as a source of vitamin $B_1$. |
| Sodium propionate | | |
| Sodium sorbate | | |
| Sodium sulfite | | Not in meats or in foods recognized as a source of vitamin $B_1$. |
| Sorbic acid | | |
| *Stannous chloride | 0.0015 percent calculated as tin. | |
| Sulfur dioxide | | Not in meats or in foods recognized as a source of vitamin $B_1$. |
| Thiodipropionic acid | Total content of antioxidants not over 0.02 percent of fat or oil content, including essential (volatile) oil content of the food. | |
| Tocopherols | | |
| (3) EMULSIFYING AGENTS | | |
| Cholic acid | 0.1 percent. | Dried egg whites. |
| Desoxycholic acid | 0.1 percent. | Dried egg whites. |
| Diacetyl tartaric acid esters of mono- and diglycerides from the glycerolysis of edible fats or oils. | | |
| Glycocholic acid | 0.1 percent. | Dried egg whites. |
| Mono- and diglycerides from the glycerolysis of edible fats or oils. | | |

| *Product* | *Tolerance* | *Limitations or restrictions* |
|---|---|---|
| (3) EMULSIFYING AGENTS —cont'd | | |
| Monosodium phosphate derivatives of mono- and diglycerides from the glycerolysis of edible fats or oils. | | |
| Propylene glycol | | |
| Ox bile extract | 0.1 percent. | Dried egg whites. |
| Taurocholic acid (or its sodium salt). | 0.1 percent. | Dried egg whites. |
| (4) NONNUTRITIVE SWEETENERS | | |
| *Ammonium saccharin | | |
| Calcium cyclamate (calcium cyclohexyl sulfamate). | | |
| Calcium saccharin | | |
| *Magnesium cyclamate (magnesium cyclohexyl sulfamate). | | |
| *Potassium cyclamate (potassium cyclohexyl sulfamate). | | |
| Saccharin | | |
| Sodium cyclamate (sodium cyclohexyl sulfamate). | | |
| Sodium saccharin | | |
| (5) NUTRIENTS AND/OR DIETARY SUPPLEMENTS[1] | | |
| *Alanine (L- and DL-forms) | | |
| *Arginine (L- and DL-forms) | | |
| Ascorbic acid | | |
| *Aspartic acid (L- and DL-forms) | | |
| *Biotin | | |
| Calcium carbonate | | |
| *Calcium citrate | | |
| *Calcium glycerophosphate | | |
| Calcium oxide | | |
| Calcium pantothenate | | |
| Calcium phosphate (mono-, di-, tribasic). | | |
| *Calcium pyrophosphate | | |
| Calcium sulfate | | |
| Carotene | | |
| *Choline bitartrate | | |
| *Choline chloride | | |
| Copper gluconate | 0.005 percent. | |
| Cuprous iodide | 0.01 percent. | In table salt as a source of dietary iodine. |
| *Cysteine (L-form) | | |
| *Cystine (L- and DL-forms) | | |
| Ferric phosphate | | |
| Ferric pyrophosphate | | |
| Ferric sodium pyrophosphate | | |
| *Ferrous gluconate | | |
| *Ferrous lactate | | |
| Ferrous sulfate | | |
| *Glycine (aminoacetic acid) | | In animal feeds. |
| *Histidine (L- and DL-forms) | | |

[1]Amino acids listed may be free, hydrochloride salt, hydrated, or anhydrous form, where applicable.

| *Product* | *Tolerance* | *Limitations or restrictions* |
|---|---|---|
| (5) NUTRIENTS AND/OR DIETARY SUPPLEMENTS[1]—cont'd | | |
| Inositol | | |
| Iron, reduced | | |
| Isoleucine (L- and DL-forms) | | |
| Leucine (L- and DL-forms) | | |
| Linoleic acid (prepared from edible fats and oils and free from chickedema factor). | | |
| Lysine (L- and DL-forms) | | |
| Magnesium oxide | | |
| Magnesium phosphate (di-, tribasic). | | |
| Magnesium sulfate | | |
| Manganese chloride | | |
| Manganese citrate | | |
| Manganese gluconate | | |
| Manganese glycerophosphate | | |
| Manganese hypophosphite | | |
| Manganese sulfate | | |
| Manganous oxide | | |
| Mannitol | 5 percent. | In special dietary foods. |
| Methionine | | Animal feeds. |
| Methionine hydroxy analog and its calcium salts. | | Animal feeds. |
| Niacin | | |
| Niacinamide | | |
| D-Pantothenyl alcohol | | |
| Phenylalanine (L- and DL-forms) | | |
| Potassium chloride | | |
| Potassium glycerophosphate | | |
| Potassium iodide | 0.01 percent. | In table salt as a source of dietary iodine. |
| Proline (L- and DL-forms) | | |
| Pyridoxine hydrochloride | | |
| Riboflavin | | |
| Riboflavin-5-phosphate | | |
| Serine (L- and DL-forms) | | |
| Sodium pentothenate | | |
| Sodium phosphate (mono-, di-, tribasic). | | |
| Sorbitol | 7 percent. | In foods for special dietary use. |
| Thiamine hydrochloride | | |
| Thiamine mononitrate | | |
| Threonine (L- and DL-forms) | | |
| Tocopherols | | |
| α-Tocopherol acetate | | |
| Trypotophane (L- and DL-forms) | | |
| Tyrosine (L- and DL-forms) | | |
| Valine (L- and DL-forms) | | |
| Vitamin A | | |
| Vitamin A acetate | | |
| Vitamin A palmitate | | |
| Vitamin $B_{12}$ | | |
| Vitamin $D_2$ | | |
| Vitamin $D_3$ | | |
| Zinc Sulfate | | |

| *Product* | *Tolerance* | *Limitations or restrictions* |
|---|---|---|
| (5) NUTRIENTS AND/OR DIETARY SUPPLEMENTS[1]—cont'd | | |
| *Zinc gluconate | | |
| *Zinc chloride | | |
| *Zinc oxide | | |
| *Zinc stearate (prepared from stearic acid free from chick-edema factor). | | |
| (6) SEQUESTRANTS[2] | | |
| Calcium acetate | | |
| Calcium chloride | | |
| Calcium citrate | | |
| Calcium diacetate | | |
| Calcium gluconate | | |
| Calcium hexametaphosphate | | |
| Calcium phosphate, monobasic | | |
| Calcium phytate | | |
| Citric acid | | |
| Dipotassium phosphate | | |
| Disodium phosphate | | |
| Isopropyl citrate | 0.02 percent. | |
| Monoisopropyl citrate | | |
| Potassium citrate | | |
| Sodium acid phosphate | | |
| Sodium citrate | | |
| Sodium diacetate | | |
| Sodium gluconate | | |
| Sodium hexametaphosphate | | |
| Sodium metaphosphate | | |
| Sodium phosphate (mono-, di,-tribasic). | | |
| Sodium potassium tartrate | | |
| Sodium pyrophosphate | | |
| Sodium pyrophosphate, tetra | | |
| Sodium tartrate | | |
| Sodium thiosulfate | 0.1 percent. | In salt. |
| Sodium tripolyphosphate | | |
| Stearyl citrate | 0.15 percent. | |
| Tartaric acid | | |
| (7) STABILIZERS | | |
| *Acacia (gum arabic) | | |
| Agar-agar | | |
| *Ammonium alginate | | |
| *Calcium alginate | | |
| Carob bean gum (locust bean gum) | | |
| Chondrus extract (carrageenin) | | |
| *Ghatti gum | | |
| Guar gum | | |
| *Potassium alginate | | |
| *Sodium alginate | | |
| *Sterculia gum (karaya gum) | | |
| *Tragacanth (gum tragacanth) | | |

[2]For the purpose of this list, no attempt has been made to designate those sequestrants that may also function as chemical preservatives.

| *Product* | *Tolerance* | *Limitations or restrictions* |
|---|---|---|
| (8) MISCELLANEOUS AND/OR GENERAL PURPOSE FOOD ADDITIVES | | |
| Acetic acid | | |
| °Adipic acid | | Buffer and neutralizing agent. |
| Aluminum ammonium sulfate | | |
| Aluminum potassium sulfate | | |
| Aluminum sodium sulfate | | |
| Aluminum sulfate | | |
| Ammonium bicarbonate | | |
| Ammonium carbonate | | |
| Ammonium hydroxide | | |
| Ammonium phosphate (mono- and dibasic). | | |
| °Ammonium sulfate | | |
| °Beeswax (yellow wax) | | |
| °Beeswax, bleached (white wax) | | |
| °Bentonite | | |
| Butane | | |
| Caffeine | 0.02 percent. | In cola-type beverages. |
| Calcium carbonate | | |
| Calcium chloride | | |
| Calcium citrate | | |
| Calcium gluconate | | |
| Calcium hydroxide | | |
| Calcium lactate | | |
| Calcium oxide | | |
| Calcium phosphate (mono-, di-, tribasic). | | |
| Caramel | | |
| Carbon dioxide | | |
| Carnauba wax | | |
| Citric acid | | |
| °Dextrans (of average molecular weight below 100,000). | | |
| Ethyl formate | 0.0015 percent. | As fumigant for cashew nuts. |
| °Glutamic acid | | Salt substitute. |
| °Glutamic acid hydrochloride | | Salt substitute. |
| Glycerin | | |
| Glyceryl monostearate | | |
| Helium | | |
| °Hydrochloric acid | | Buffer and neutralizine agent. |
| °Hydrogen peroxide | | Bleaching agent. |
| Lactic acid | | |
| °Lecithin | | |
| Margnesium carbonate | | |
| Magnesium hydroxide | | |
| Magnesium oxide | | |
| Magnesium stearate | | As migratory substance from packaging materials when used as a stabilizer. |
| °Malic acid | | |
| °Methylcellulose (U.S.P. methylcellulose, except that the methoxy content shall not be less than 27.5 percent and not more than 31.5 percent on a dry-weight basis). | | |

| *Product* | *Tolerance* | *Limitations or restrictions* |
|---|---|---|
| (8) MISCELLANEOUS AND/OR GENERAL PURPOSE FOOD ADDITIVES—cont'd | | |
| Monoammonium glutamate | | |
| *Monopotassium glutamate | | |
| Nitrogen | | |
| *Nitrous oxide | | Propellant for certain dairy and vegetable-fat toppings in pressurized containers. |
| Papain | | |
| Phosphoric acid | | |
| Potassium acid tartrate | | |
| Potassium bicarbonate | | |
| Potassium carbonate | | |
| Potassium citrate | | |
| Potassium hydroxide | | |
| *Potassium sulfate | | |
| Propane | | |
| Propylene glycol | | |
| *Rennet (rennin) | | |
| *Silica aerogel (finely powdered microcellular silica foam having a minimum silica content of 89.5 percent). | | Component of anti-foaming agent. |
| Sodium acetate | | |
| Sodium acid pyrophosphate | | |
| Sodium aluminum phosphate | | |
| Sodium bicarbonate | | |
| Sodium carbonate | | |
| Sodium citrate | | |
| *Sodium carboxymethylcellulose (the sodium salt of carboxymethylcellulose not less than 99.5 percent on a dry-weight basis, with maximum substitution of 0.95 carboxymethyl groups per anhydroglucose unit, and with a minimum viscosity of 25 centipoises for 2 percent by weight aqueous solution at 25° C.). | | |
| *Sodium caseinate | | |
| Sodium citrate | | |
| Sodium hydroxide | | |
| *Sodium pectinate | | |
| Sodium phosphate (mono-, di-, tribasic). | | |
| Sodium potassium tartrate | | |
| Sodium sesquicarbonate | | |
| Sodium tripolyphosphate | | |
| *Succinic acid | | |
| Sulfuric acid | | |
| Tartaric acid | | |
| Triacetin (glyceryl triacetate) | | |
| Triethyl citrate | 0.25 percent. | Dried egg whites. |

## Book reviews

**The Human Blood Proteins**, by F. Wuhrmann and C. Wunderly. London, 1960, Grune & Stratton, Inc. 491 pages. $15.75.

H. T. Adelson's translation of the third edition of the Wuhrmann and Wunderly book is a valuable contribution to the clinical study of blood proteins. The authors feel that the technique of paper electrophoresis combined with cellular findings and clinical lability tests gives the clinician a more objective evaluation of protein changes in chronic processes as well as in conditions exhibiting a primary derangement of the protein picture. Considerable emphasis is placed on these protein profiles and shifts in these profiles on repeated testing to indicate not only the type of the reactive response but also to check on the change in the disease state. The paper electrophoresis pattern, the erythrocyte sedimentation reaction, the Weltmann cogulation bond, the nephalogram method, and the turbidity and flocculation reactions are the tests considered in determining the type of reaction response. For any type of reaction grouping presented, whether it be of an acute inflammatory type or of an obstructive jaundice type, the observations and analysis are supported by data from the extensive case material of the Cantonal Hospital in Winterthur-Zurich.

Although the largest section of the book is devoted to the clinical significance of plasma proteins, an equally interesting section is presented on dysproteinemia and paraproteinemia. Within the fibrinogen fraction, states such as hyperfibrinogenemia, fibrinopenia, and afibrinogenemia are considered. Changes in the individual components of the globulin fractions are considered, followed by examples of special disease pictures on conditions such as plasmocytoma, macroglobulinemia, and hyperproteinemia in chronic inflammatory processes. The albumin fraction is also thoroughly considered, with examples of disease pictures such as the nephrotic symptom complex, chronic liver disease, and derangements of the gastrointestinal tract.

In the new edition, sections on paper chromatography and spectrophotometry are omitted; however, the section on the ultracentrifuge technique is retained. The references are extensive and international in scope and are quoted and interpreted succinctly. This excellent translation of a classic work in the field is readable and informative without being cumbersome.

*Joseph F. Reilly*

**Quantitative Methods in Pharmacology,** edited by H. De Jonge. New York, 1960, Interscience Publishers, Inc. Amsterdam, North-Holland Publishing Company. 391 pages. $13.25.

In twenty-five articles presented at the Symposium on Quantitative Methods in Pharmacology held in 1960 under the sponsorship of the Biometric Society, this book reveals a most informative account of the dynamic state and of the developmental forces in quantitative pharmacology. The presentations encompass practical issues of design and efficiency of bioassays in animals and man, as well as advanced considerations in statistical theory and modern formulations of the drug-receptor hypothesis. In fact, it appears to have been the plan of the Symposium to harmoniously blend practice and theory of biostatistics, and in this the Symposium was very successful.

In an introductory address, Freudenthal condensed in a few pages a profound and witty historical survey on mathematical statistics; he reveals many important insights, and outstanding among these is the clear formulation of the innovation which originated with Thomas Bayes and, in turn, led to the Neyman-Pearson theory and, finally, to Wald's betting model. Some articles in this book clearly indicate a trend in biostatistics to replace the classic "urn model" with a model taken from statistical decision theory: its application to the choice of sequential procedures (Johnson) and to drug screening (Dunnett) are notable examples of this trend. Attempts to incorporate changes of dose into sequential tests (Rümke) lead to a two step assay procedure, the first step of which is nearly identical with the method of successive approximation first proposed by S. Loewe in a generally (and also to the author of this article) unknown abstract (J. Pharmacol. & Exper. Therap. 66:23, 1939). The statistics of quantal responses is carefully discussed under the chairmanship of Emmens. Six papers are devoted to a comparative evaluation of parametric and nonparametric statistical methods, with special emphasis on the comparison between Student's and Wilcoxon's tests. In a succinct summary of the present views on receptors, Schild introduces the articles dealing with formal description and mechanistic aspects of drug interactions. Brock and Schneider expose the deeply rooted ambiguities of the "therapeutic index" and outline the necessary remedies.

Statistical theory would predict that the conglomeration of so many pertinent, valuable, and informative papers in one volume constitutes a most unlikely event, unless some Maxwell demon intervened; Professor De Jonge, as editor, obviously performed this function most successfully.

*Gerhard Werner*

**Enzymes in Clinical Medicine,** by Irving Innerfield. New York, 1960, McGraw-Hill Book Company, Inc. 334 pages. $11.50.

"This enzyme," said the bright young man, "will benefit all your patients with inflammation of whatever nature."

"But how does it do it?" said the old fogy, puffing at his pipe.

"Among other things it destroys polypeptides which aggravate the inflammatory process, thus allowing speedy natural resolution."

"What evidence do you have that it is clinically effective?" said the old man, releasing clouds of smoke.

"Various people have reported that inflammation comes to a head and the pus can be incised and drained within forty-eight hours; in fact, this is so reliable that they can predict that incision can take place within forty-eight hours of receiving the enzyme."

"But, my dear man, I remember quite a number of my patients who had never heard of enzymes where the same thing

happened. You know, I think you may be overlooking the natural history of disease."

The author of this book has put a great deal of work into it, and the first section, dealing with the biochemical and pathologic background, is very full; too full, in fact, and there are so many reports of different research projects that only someone intensely interested in this field will find it useful. The organization is poor, and there is much confusion. The author has the peculiar habit of giving important general information at the end of a chapter or section, when this would be better placed as an introduction to that particular section, with experimental work following.

The above criticism is minor as compared to the main one: the author is not at all objective in reporting and evaluating results from the literature. To some extent this is understandable, since he was one of the pioneers in the clinical use of enzymes and is a great protagonist for their use. However, overenthusiastic supporters will not advance the cause of enzyme therapeutics by presenting inadequate clinical evidence. The following statement was found on page 126:

"Following intravenous trypsin . . . seven patients with influenza showed dramatic drops in temperatures within forty-eight hours, as well as definite clinical improvement."

Not recommended.

*Edel Berman*

**Annual Review of Physiology**, Volume 23, edited by V. E. Hall. Palo Alto, 1961, Annual Reviews, Inc. 674 pages. $7.00.

In the prefatory chapter written by Dr. Carl Schmidt (Emeritus Professor of Pharmacology, University of Pennsylvania, School of Medicine) entitled "Pharmacology in a Changing World," pharmacology is characterized as the discipline which is concerned with the use of drugs to dissect out physiologic mechanisms, the description of drugs and their uses for the orientation of the physician, and the discovery and evaluation of new therapeutic agents.

Dr. Schmidt turn his attention on the present and future particularly to the recruitment of investigators and bemoans the fact that it is likely that many of the better undergraduate candidates go into biochemistry and physiology rather than pharmacology. This he attributes to the lack of familiarity of high school and college science teachers and, consequently, the undergraduate student with pharmacology. Accordingly, Dr. Schmidt seems to feel that graduate training programs in pharmacology will not be highly successful and that the medical graduate would serve as a more likely source for the future leaders of pharmacology. He recognizes that there are many obstacles to overcome in recruiting qualified medical graduates. It is pointed out that modern clinical departments provide opportunities nearly equal to those found in the basic departments for intellectually stimulating experiences and that contact in medical school with basic departments is generally so brief that it hardly provides sufficient exposure. While Dr. Schmidt feels that the disparity in salary between the preclinical and clinical departments has been narrowed, it is the reviewer's opinion that it is still large enough to dull the interest of young medical school graduates in a career in basic medical sciences. Neither does it seem likely that this difference will become less significant in the near future. It would appear that the undergraduate student is still the more likely candidate for recruitment, and if there were undergraduate courses in pharmacology, the difficulty in recruiting qualified graduate students would be largely resolved.

Dr. Schmidt makes the pertinent closing points that pharmacology serves as a final common pathway for all medical sciences and that, to continue in this role, it is necessary to have diversification in its conceptual and operational aspects.

The review of the chapters devoted to specific physiologic systems must be limited to the interest and competence of the reviewer. Hoffman and Kavaler considered the recent developments in pharmacology and physiology of the heart. In addition to transmembrane potentials, excitability, and disorders in rhythm, there is a section on the important question of the syncytial nature of cardiac muscle. Investigations of ions and excitation-contraction coupling are also summarized.

The chapter by Frank and Fourtes on excitation and conduction is notable for its highly critical treatment of the role ascribed to synaptic potentials. Three main tenets of the work of Lloyd and his coworkers were examined: (1) excitatory postsynaptic potentials are not the cause of reflex excitation, (2) excitation and facilitation are caused by different processes, probably by different presynaptic actions, and (3) reflex inhibition is not caused by the inhibitory postsynaptic potential. The critical discussion of these points is both lively and informative.

The chapter on transmitter substances was equally stimulating since Ernst Florey made it a point to interject his own views in summarizing the recent literature. Dr. Florey cautions against the assignment of a physiologic role to acetylcholine on the basis of its occurrence. It is pointed out that many cholinesters have been found in tissues and that unless chemical identification supplements the bioassays, it is difficult to decide whether an acetylcholine-like action is caused by it or another cholinester. Furthermore, he appropriately points out that finding cholinesterase activity does not necessarily imply acetylcholine is the transmitter, since this common enzyme system may well be involved in functions other than acetylcholine hydrolysis. The section concerned with theoretic considerations of the concept of chemical transmission is highly recommended.

The data on the nervous system, somatic, visceral, and central, are extensive and well documented. Topics considered in this issue which were not specifically covered in last year's *Annual Review* are energy metabolism, transport through biologic membranes, comparative physiology, photoperiodicity, physiologic aspects of aging in man, liver, skin, hearing, transmitter substances, and major problems in muscle physiology.

*Jay Roberts*

**A Physician's Introduction to Electronics: A Laboratory Manual,** by A. C. Morris, Jr. Oxford, 1961, Pergamon Press Ltd. 43 pages. $2.50.

The title of this book is a misnomer. The subtitle is much more accurate. It is essentially a set of instructions for the use of a particular piece of electronic hardware: the Oak Ridge Institute of Nuclear Studies (ORINS) electronic breadboard. Unless one happens to have this piece of equipment, he is unlikely to have any use at all for this publication.

*Frank G. Standaert*

**An Introduction to the Experimental Method,** by J. M. Little. Minneapolis, 1961, Burgess Publishing Company. 84 pages. $3.00.

I commend this book to all first, second, third, and fourth year medical students as well as to all physicians not experts in experimental medicine who would perform or even read critically about experiments.

Unlike the currently available larger books bound between hard covers, this small, soft cover monograph is neither ponderous nor portentous but deals deftly with its subject, using the light touch. Through neat discussion of general principle as well as by clear and simple example without recourse to complex mathematics or ob-

secure manipulation, it makes clear many statistical concepts which are surely murky to most physicians and medical students. Everything is somehow made to reveal its own inner workings, from the standard error of the mean to the analysis of variants. Thus, a basic understanding of standard statistical methods can be readily attained and to a limited degree even employed.

The monograph will not make a statistician of anyone, and it is certainly not a book for one who needs no help in elementary statistics or experimental design, but it is the book for a large number of us.

*Walter Modell*

**Drugs in the Treatment of Disease.** London, 1961, British Medical Association. 516 pp.

I have written a vigorous and most uncomplimentary review of this book for another journal. Although on second reading I have not had the slightest change of heart, I am constrained to forbearance and therefore will not attack *Drugs in the Treatment of Disease*, while it is down. Those who are interested in my views are referred to the review in the *A.M.A. Archives of Internal Medicine.*

*Walter Modell*

## Books received

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## Drug therapy and the geriatric patient

At present, a great deal of attention is being focused on the medical problems of the aged. Among the many facets of the problem is that of drug therapy. The rapid development of new drugs for almost every therapeutic need has made available many new agents. Although, for the most part, these substances can be used satisfactorily in older patients, there are certain situations which must be considered and which, if neglected, can and do lead to unsatisfactory or undesirable results.

In spite of the strong desire of older persons not to be isolated in any way from the mainstream of human activities, it is necessary to treat them somewhat differently in certain situations, because of their changed biologic status. Particular characteristics of aged persons must be considered carefully if they are to secure the maximum benefit from drug therapy.

1. Therapy should be fitted into the patient's mode of life—it is too much to expect an aged patient to change his pattern of living in order to obtain what may seem to be questionable benefits from the use of a drug.

2. Drug therapy in the older patient should be simple in character—complex dosage patterns, gadgets which are difficult to operate, inaccurate measuring of liquids, and lack of detailed information will often lead to failure and possibly to toxic reactions.

3. The physician must use care in the handling of established drug habits even though he knows the agent being taken can be of no pharmacologic use to the patient. Unfortunately, the placebo value of cathartics, sedatives, aspirin, vitamin mixtures, and a host of other agents commonly taken may be very great, and sudden termination of their use may produce surprising complications. Older persons must be weaned carefully but firmly from agents potentially harmful to them. Frequently, this process requires considerable reassurance and much tact and patience on the part of the physician.

4. Drugs should be selected with certain points in mind. Most situations are likely to be chronic and to require long-continued therapy. It is, therefore, essential at the outset to select agents which are not cumulative, which have low addiction potential, which are resistant to tissue tolerance or to which tolerance develops slowly, which have low inherent toxicity, and, finally, which are the most effective and least expensive.

5. Knowledge of certain physiologic and pharmacologic factors is essential to proper use of drugs in the elderly. As the individual ages, certain physiologic changes occur which profoundly affect pharmacologic response to drugs. Functional reserve is progressively lost: muscles are unable to perform as much work; cardiac reserve is markedly reduced, and the heart cannot meet sudden severe demands or maintain long-continued increased work loads; much renal reserve is lost, and the kidneys, although performing normally, are incapable of meeting severe or long-continued stress situations. Unquestionably, there are other factors at present not recognized or poorly understood which also influence the outcome of drug therapy. It is, therefore, wise for the physician to use a new drug cautiously until he determines the elderly patient's response to its action.

6. As age progresses, degenerative diseases commonly appear, and these further complicate therapy. An eye which tolerated atropine or other mydriatic agents at age 30 may, because of slowly developing glaucoma, be seriously damaged by these agents at 70. Impaired cerebral circulation may be asymptomatic until cerebral tissue is under stress or irritated by drug action. Likewise, a heart with asymptomatic atherosclerosis may be seriously damaged by sudden falls in blood pressure caused by hypotensive agents.

7. Drugs frequently lead to abnormal psychologic responses in the elderly patient. It is well recognized, for example, that phenobarbital, probably by virtue of its cerebral depressant effect, may cause confusion, excitement, and agitation in the elderly patient. This reaction occurs so frequently that the careful physician avoids its use in geriatric patients. Many of the agents to counteract parkinsonism result in abnormal mental behavior in older patients, as do some of the atropine-like gastrointestinal antispasmodic drugs.

8. The bowels and the urinary bladder are apt to cause difficulty in the elderly patient who is receiving drugs. Prostatic obstruction in the male or a relaxed sphincter or cystocele in the female is likely to cause difficulty whenever drugs are given which increase or decrease tone of smooth muscle. Interference with the function of either bladder or bowel may be a source of annoyance and may lead to serious consequences. Straining at stool following drug-induced constipation may set in motion a serious chain of events. Likewise, a relaxed atonic bladder may lead to urinary tract infection, and serious complications may follow. Agents for parkinsonism, gastrointestinal antispasmodics, iron and iron-vitamin mixtures, cathartics, and certain antacids are common offenders in these respects and must be used with care in older patients.

9. Finally, some thought must be given to the cost of drug therapy. Frequently, the condition being treated is chronic, and therefore drugs will have to be taken for long periods. Much has been said about the lowered income of retired older persons living on pensions or being helped by others, so that we are all aware that many in this group cannot afford expensive therapy for long periods of time. It is, therefore, necessary for the physician to make certain not only that he is prescribing the most effective agent but also that he is not being wasteful by overprescribing or continuing drugs unnecessarily. Frequently, less expensive drugs can be used as the patient improves. It is, indeed, futile to prescribe an expensive preparation which the patient cannot afford and, therefore, will not take, when another, less expensive, although perhaps not quite as effective, agent which the patient can afford and will take is passed over.

Based on my own experience during 25 years of service as physician to an institution for aged men, certain patterns of drug action in elderly patients have become evident. These observations have been helpful in avoiding untoward drug effects and in the selection of the most effective drugs. A brief summary of these observations arranged according to classes of drugs may prove useful.

### *Sedative hypnotic drugs*

Use care in prescribing any long-acting, slowly metabolized drug in this series. Choral hydrate is frequently well tolerated and effective. Often the tranquilizers, such as meprobamate and prochlorperazine and related phenothiazines, prove most useful. Frequently, a sedative combined with an analgesic is much more effective than either alone.

### *Antiparkinsonism drugs*

Start dosage carefully, and gradually increase it. Check eye pressure tonometrically, and make certain bowel and bladder are functioning properly. Sudden confusion, excitement, disorientation, or other psychologic aberrations are probably drug effects. Change to another drug as the dose of the offending one is reduced and discontinued. Never leave the patient under no drug therapy at all while changing drugs. This may cause serious discomfort and result in a patient with parkinsonism who will never recover his original status.

### *Antihypertensive drugs*

Altogether too many elderly patients with high systolic and normal or only slightly elevated diastolic pressure receive antihypertensive therapy. No drugs now available will relax thickened, stiff, or calcified arteries which are responsible for the increased systolic pressures. Such agents can and frequently do lead to complications. In spite of the usually benign effects of reserpine, it can, in the elderly, create much emotional distress and has led to syncope, weakness, and at times even more serious consequences. In my experience, the thiazide diuretics are more likely to lead to complications in the elderly patient. Potassium loss seems to be observed more often, and cardiac arrhythmias appear more frequently. These may be consequences of impaired renal functional reserve seen in older patients. It is a point that deserves more thorough study.

### *Cardiac glycosides*

Although the usual toxic signs are commonly seen, there are at least three toxic effects that occur more commonly and more subtly in the older patient. Instead of the usual nausea and vomiting, these patients tend to develop anorexia. They lose their appetites over a period of some weeks and may gradually lose weight. Appetite and weight return to normal when the drug is stopped and dosage is subsequently reduced.

Visual effects are also not clear cut. Instead of "color" vision, older patients develop what they call "muddy" or hazy vision, which on close questioning may be described as slightly brownish or yellowish. This toxic effect may lead to visual complaints; the patient may ask for new glasses or a checkup of his eyes since he cannot see things as clearly as before. It may take several days for the visual disturbance to clear once the drug is discontinued. Finally, arrhythmias seem to appear without other signs of toxicity and may be the first evidence of overdosage. Unfortunately, they tend to persist longer than in younger patients. For this reason, I have found it more satisfactory to use the more readily eliminated digoxin in elderly patients. The powdered leaf, which contains digitoxin, and crystalline digitoxin are more likely to cause difficulty, and once toxicity occurs, it persists for a longer time.

### *Analgesic agents*

The use of aspirin is common in older patients. They are invariably convinced that it is a harmless drug and use large amounts for almost every ache and pain. Unfortunately, many have developed a habit of taking one or two and occasionally more aspirin tablets on retiring. They find that they relax and sleep better. There may be some merit to this use of an analgesic on retiring. Tired,

aching muscles, arthritic joints, inflamed ligaments, and ischemia of tissue resulting from poor circulation create discomfort which prevents sleep or leads to intermittent sleep. Frequently, limbs so afflicted are irritated, and muscle cramps may develop. Paresthesia appears, and sleep is lost. Therefore, an analgesic at bedtime is often far better than a sedative. However, the continued use of aspirin on an empty stomach at bedtime is a common cause of gastric irritation. It leads to indigestion and, more serious, loss of blood and sometimes frank hemorrhage. In a period of 6 months, I hospitalized 3 elderly patients with severe gastrointestinal bleeding which, after thorough study, was diagnosed as gastritis secondary to aspirin irritation. All 3 had been taking aspirin at bedtime on an empty stomach. Recent studies have shown that certain aspirin tablets are highly irritating to gastric mucosa while others made by experienced manufacturers are far less irritating. It is evident that aspirin should not be taken on an empty stomach; some food should first be taken, and the patient should crush the tablet before swallowing.

The long-continued use of analgesics containing phenacetin and acetanilide may lead to mild anemia as well as gastric irritation; this practice should be discontinued.

Codeine, even in the small doses used in cough syrups, may lead to serious difficulty in older patients. It frequently causes nausea and at times vomiting. This can be a serious complication in a feeble arteriosclerotic individual. Constipation and urinary retention in the male may also follow. These complications are unpleasant and may cause much distress, and straining efforts to empty bowel or bladder are definitely undesirable.

### *Gastrointestinal drugs*

Older patients are prone to indigestion, pyrosis, gas, bloating, and belching, and they may use large amounts of sodium bicarbonate. Although this gives quick relief, it is likely to create more gas and frequently lead to further distress. The real problem, of course, is the excess sodium intake, with the resultant load on the circulation and kidneys. In the older patient, this can be serious, and I have seen congestive failure follow such use of sodium bicarbonate.

Unquestionably, the most widespread problem is that of cathartics. Approximately 65 per cent of all patients complain of constipation and feel that they must take some drug for relief. In the older age group, there is much greater concern with elimination, and it is a rare patient who does not have his favorite cathartic. These range from mild bulk producers to the highly irritant organic vegetable preparations. Frequently, irritant cathartic action coupled with the common bowel lesion of diverticulosis results in a bowel cripple. These patients, with their intractable constipation, severe pains in the lower abdomen, and at times bleeding into the bowel, are commonly seen by the physician.

### *Antibacterial agents*

Most anti-infectious agents are well tolerated, but there are a few situations in which caution is in order. The long-acting sulfa drugs which are slowly eliminated by the kidney have a somewhat greater tendency to accumulate in the elderly patient. This is probably secondary to reduced renal reserve. It can lead to gastrointestinal disturbances, although no toxic effects of consequences have so far been observed.

The broad spectrum of antibiotics, especially of the tetracycline series, may lead to severe pruritus ani or vulvae which, unfortunately, tends to persist for long periods of time. This reaction is more common in the elderly possibly because of local skin atrophy.

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# CLINICAL PHARMACOLOGY and THERAPEUTICS




**Volume 2, January-December, 1961**

**The C. V. Mosby Company, St. Louis**

Volume 2


*Printed in the United States of America*

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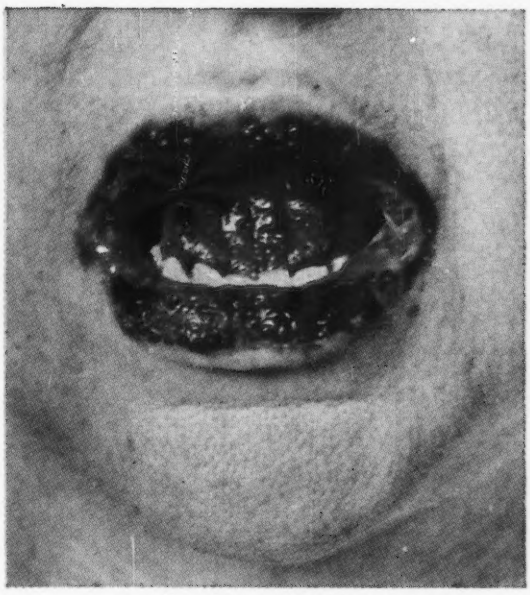
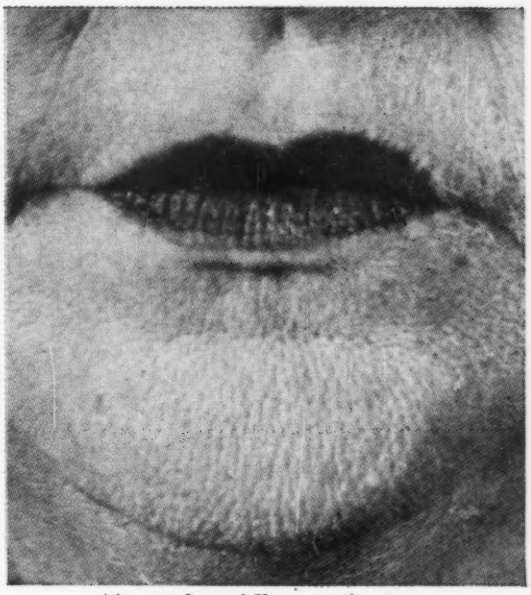


*Pemphigus vulgaris*



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*References:* 1. Edelstein, A J.: Pennsylvania M. J. *62*:1831 (Dec.) 1959. 2. Smith, J. G., Jr.; Engel, M. F.; and Blank, H.: J. Florida M. A. *46*:960 (Feb.) 1960. 3. Robins, H. M.: New York J. Med. *61*:717 (Mar. 1) 1961.

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